4 Natural Products, a Potential Source of New Drugs Discovery to Combat Obesity and Diabetes: Their Efficacy and Multi-targets Actions in Treatment of These Diseases

Biswanath Dinda and Manikarna Dinda

4.1 Introduction

Since the prehistoric times, at least 60,000 years back as per fossil records, humans have been using natural products, such as plants, animals, microorganisms, and marine organisms, in medicines to alleviate and treat diseases. The use of natural products as medicines must have a great challenge to early humans because when seeking food in forests and hills, early humans often consumed poisonous plants, which led them to vomiting, diarrhea, coma, or other toxic reaction-even death. Subsequently, they were able to develop knowledge about edible plant materials and to use many plants as natural medicines for treatment of diseases and ailments, which are the basis of traditional medicine. Such forms of traditional medicines, namely, traditional Chinese medicine (TCM), Indian Ayurveda, Greek-Arabic Unani, Japanese Kampo, and traditional Korean medicine, known as Sasang constitutional medicine (SCM) have been practiced worldwide for more than thousands of years and have blossomed into the present systems of modern medicines. The advancement of modern technology helped us to evaluate the pharmacology and mechanism of action of many medicinal herbs in treatment of diseases and to use them as cornerstones of modern medicine. In the historic year 1805, German pharmacist Friedrich Serturner isolated morphine from the opium plant, *Papaver somniferum* L., and laid the foundation of modern medicine. Subsequently, countless active natural molecules, known as phytochemicals have been separated from natural plant and microbial extracts, and many of them have potential anticancer, antihypertensive, hypolipidemic, antiobese, antidiabetic, antiviral, antileishmanial, and antimigraine

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medicative properties. These phytochemicals, which have evolved over millions of years, have a unique chemical structural diversity, which results in the diversity of their biological actions to alleviate and treat critical human diseases. A group of evidence advocates that a "multidrugs" and "multi-targets" approach would be more effective compared to a "single-drug" and "single-target" approach in the treatment of complex diseases like obesity, diabetes, cardiovascular disease, and cancer. Phytochemicals present in a single herb or in a herbal formulation can function alone or synergistically with other phytochemicals in a "multi-targets" approach to produce desired pharmacological effect in prevention and cure of complex diseases. The optimal efficacy of the herbal/polyherbal extract depends on its correct dosage containing the optimal concentration of bioactive phytochemical (s) and the method of preparing and processing of the herbal/polyherbal composition and the appropriate time of collection of plant parts. Therefore, the research on natural products is a thrust area for future research in drug discovery (Yuan et al. 2016). This chapter summarizes the current progress in the study of the antiobesity and antidiabetic potentials of natural products and their main bioactive phytochemicals, major molecular mechanisms in preventing and treating obesity and diabetes, and their associated complications.

4.2 Natural Products in Human Health Care and Diseases

Natural products such as plants, animals, microorganisms, and marine organisms have been used by humans since the prehistoric times. As per records identified in the fossils, primitive humans have used some edible plants for treatment of diseases and minor illnesses from at least 60,000 years ago (Fabricant and Farnsworth 2001). Possibly, on eating these toxic plants as their diet, they experienced various adverse effects, such as vomiting, diarrhea, coma, and other toxic reactions, which led them to acquire knowledge on the medicinal properties of these edible plant materials. Subsequently, humans have made technological breakthroughs and developed methods of processing of these plant materials and to use them in traditional medicine for treatment of diseases and primary health care. As per literature evidence, natural products based traditional medicines, such as Indian Ayurveda, traditional Chinese medicine (TCM), Greek Unani in Greece and Islamic world, traditional Japanese medicine, Kampo, traditional Korean medicine known as Sasang constitutional medicine (SCM), traditional African medicine, traditional Aboriginal medicine of Australia, and Russian herbal medicine have been practiced all over the world for more than thousands of years and have blossomed into orderly regulated systems of natural medicines. In spite of certain defects on correct doses, safety, and efficacy of these medicines, these traditional medicines are in the backfoot of modern medicine (Alves and Rosa 2007). Natural products, namely, plants, marine algae and animals, microorganisms living in different habitable environments in both land and water mass, experienced many stresses, challenges, and attacks from harmful microbes and animals. To get rid off from these threats, these natural organisms have developed some tiny molecules, known as

phytochemicals, such as alkaloids, flavonoids, phenolic acids, glucosinolates, terpenoids, tannins, antibiotics, and others for their survival. These phytochemicals have reverse pharmacology of the diseases. Because of local availability and low cost, natural products have been playing a vital role in primary health care among unprivileged sections of people in the world. Over 70–95% of the population in Africa, Asia, Latin America, and Middle East use some form of traditional medicine as their first line of choice in primary health care. Several hospitals and clinics recommend herbal medicines for maintenance of good health, for alleviation of chronic diseases, and rarely for acute and life-threatening diseases (Robinson and Zhang 2011). About 40% of recent drugs in clinical practice have been developed from natural products. Several phytochemicals isolated from plants, animals, and microorganisms have made revolutions in modern medicine. Among them, pain killer alkaloid, morphine (**1**, Fig. 4.1) from opium plant, *Papaver somniferum*, anticancer diterpenoid taxol (**2**) from *Taxus brevifolia*, antileukemic alkaloids vincristine (**3**) and vinblastine (**4**) from *Catharanthus roseus* syn. *Vinca rosea*, anticancer alkaloid doxorubicin (**5**) from *Streptomyces peucetius*, antimalarial alkaloid quinine (**6**) from *Cinchona* spp., antimalarial sesquiterpene lactone, artemisinin (**7**) from *Artemisia annua*, antidiabetic flavonoid glycoside, puerarin (**8**) from *Pueraria lobata*, hypolipidemic polyphenolic curcumin (**9**) from *Curcumin longa*, anti-gastric-ulcer sesquiterpene lactone, costunolide (**10**) from *Saussurea lappa*, anti-hypercholesterolemic hexahydronaphthalene delta-lactone compound, lovastatin (**11**) from *Aspergillus terreus*, antibiotic tetracycline (**12**) from *Streptomyces aureofaciens*, pancreatic lipase inhibitor, a-four-membered-cyclic-beta-lactone lipstatin (**13**) from *Streptomyces toxytricini*, antibiotic cyclosporine (**14**) from *Tolypocladium inflatum*, antimuscarinic (anticholinergic) alkaloid, atropine (**15**) from *Atropa belladonna*, muscle-relaxant alkaloid, curare (**16**) from *Chondrodendron tomentosum*, antihypertensive L-proline derivative, captopril (**17**) from Brazilian viper, *Bothrops jararaca*, antidiabetic GLP-1 agonist peptide, exenatide (**18**) from lizard, *Heloderma suspectum* are significantly noted ones (Weibel et al. 1987; Dar et al. 2017; Thomford et al. 2018; Calixto 2019). It inspired the pharmaceutical industries for the discovery of bioactive natural products, and several natural molecules were reported as new drugs for treatment of life-risk diseases (Newman et al. 2003). However, at the beginning of the twenty-first century, several synthetic compounds related to the structures of natural products (natural molecules) were found to have better efficacy compared to natural molecules. As a result, most of the pharmaceutical industries and drug discovery-related research institutes have paid their attention for the development of synthetic drugs and reduced their efforts in the discovery of natural molecules (Li and Vederas 2009). After a couple of years, most of the synthetic drugs have been shown to exhibit many odd effects in patients and were withdrawn from the market. It provoked these pharmaceutical industries to search for discovery of natural molecules with minimum adverse effects in patients. A recent report on new drugs from natural resources demonstrated that about 40% of drugs were from natural products in the years 2000–2008, which dropped to about 20% in 2009, followed by

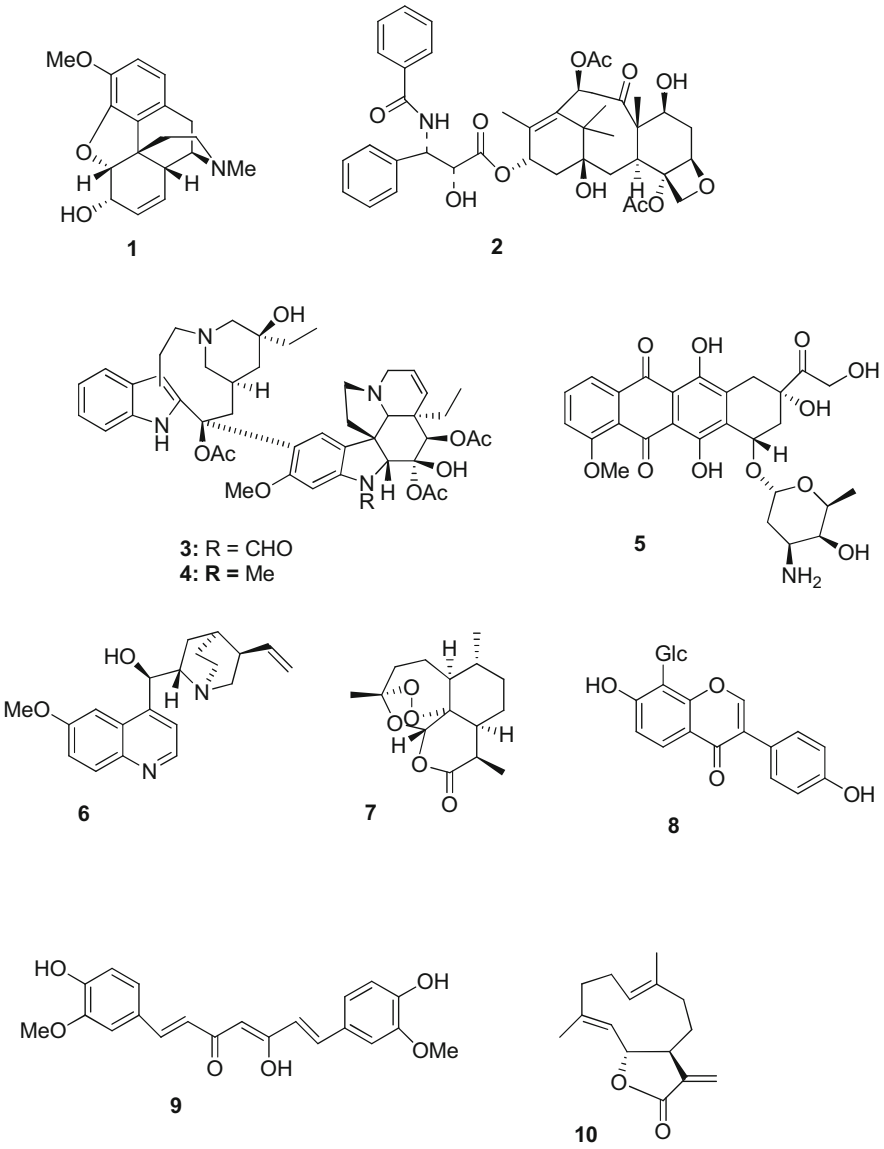
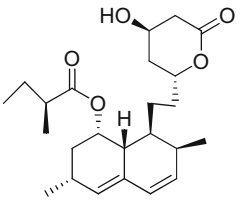


Fig. 4.1 Chemical structures of some natural products



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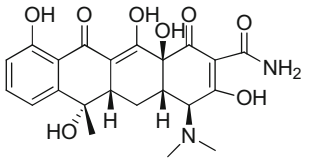

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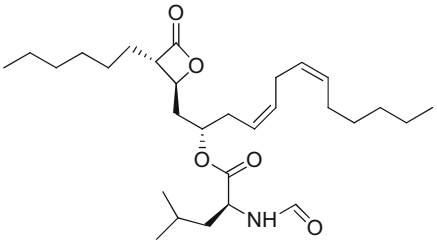

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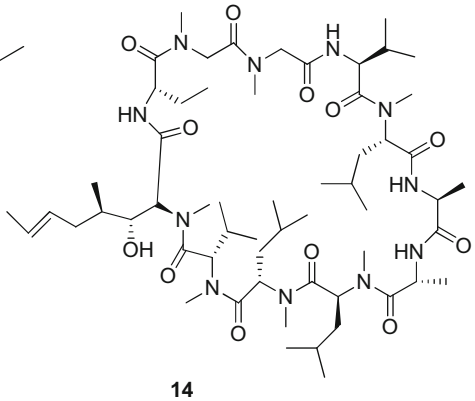

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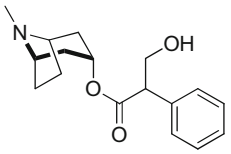

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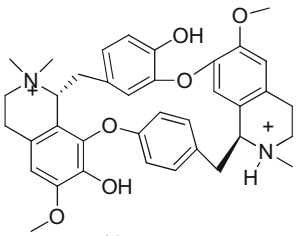

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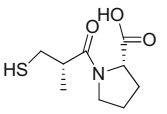

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H-His-Gly-Glu-Gly-Thr-Phe-Thr-
-Ser-Asp-Leu-Ser-Lys-Glu-Met-
-Glu-Glu-Glu-Ala-Val-Arg-Leu-
-Phe-Ile-Glu-Try-Leu-Lys-Asn-
-Gly-Gly-Pro-Ser-Ser-Gly-Ala-
-Pro-Pro-Pro-Ser-NH_2

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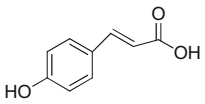

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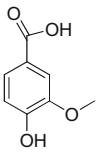

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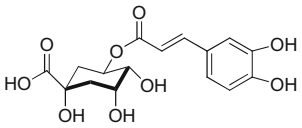

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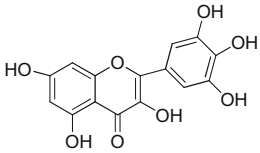

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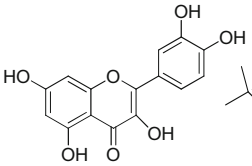

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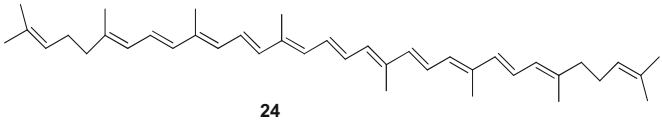

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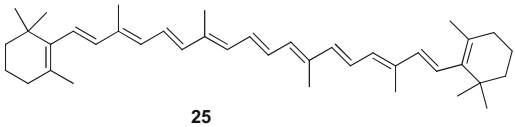

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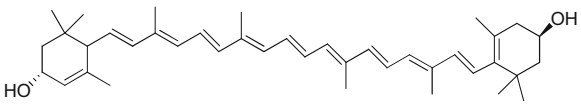

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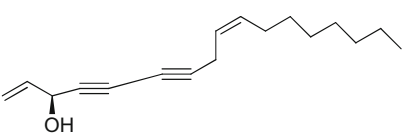

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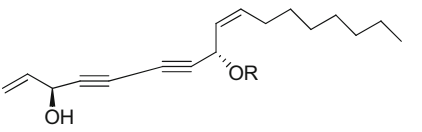
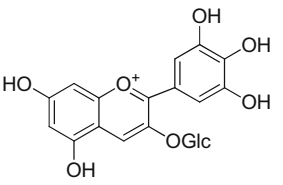


28: R = H
29: R = Ac



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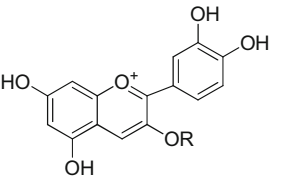
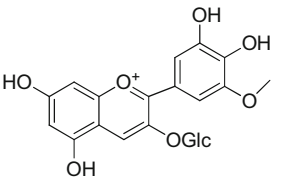


31: R = Glc
31a: R = Glc(6-1)-Rha



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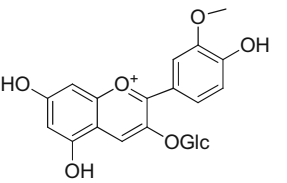

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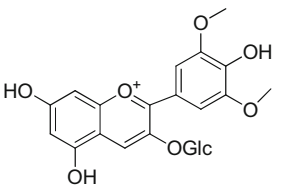

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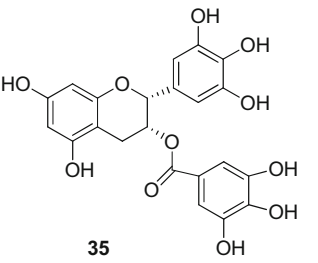

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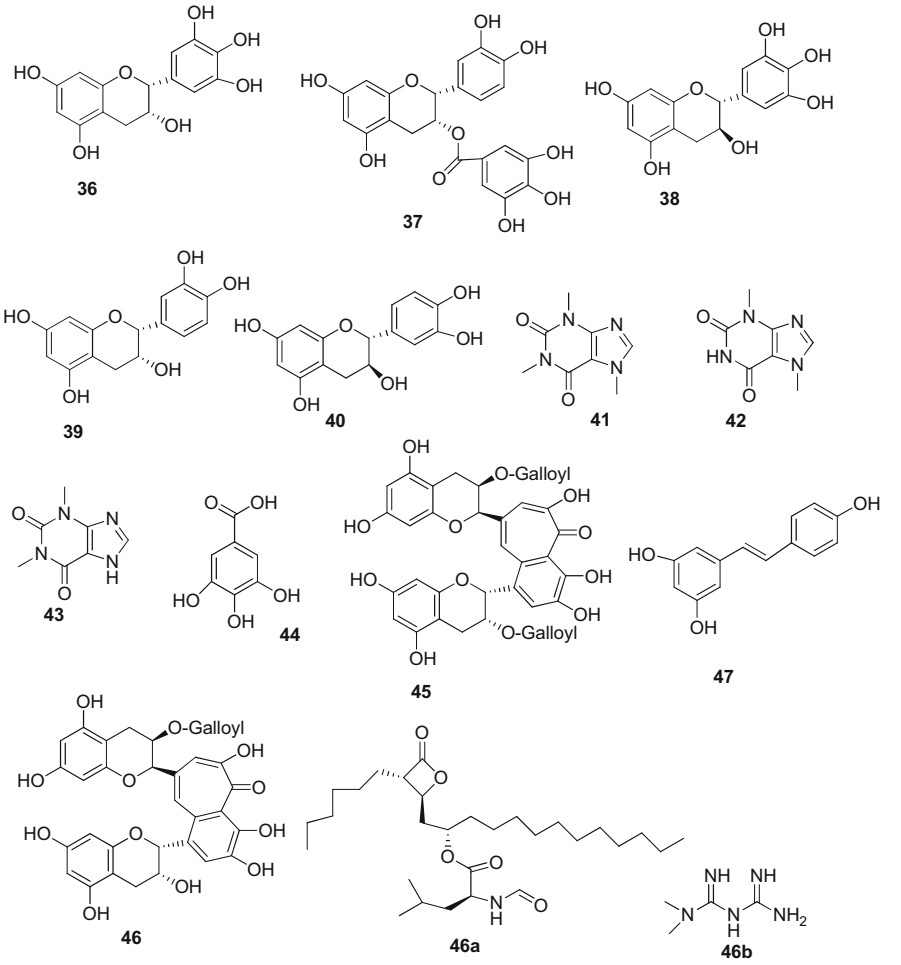

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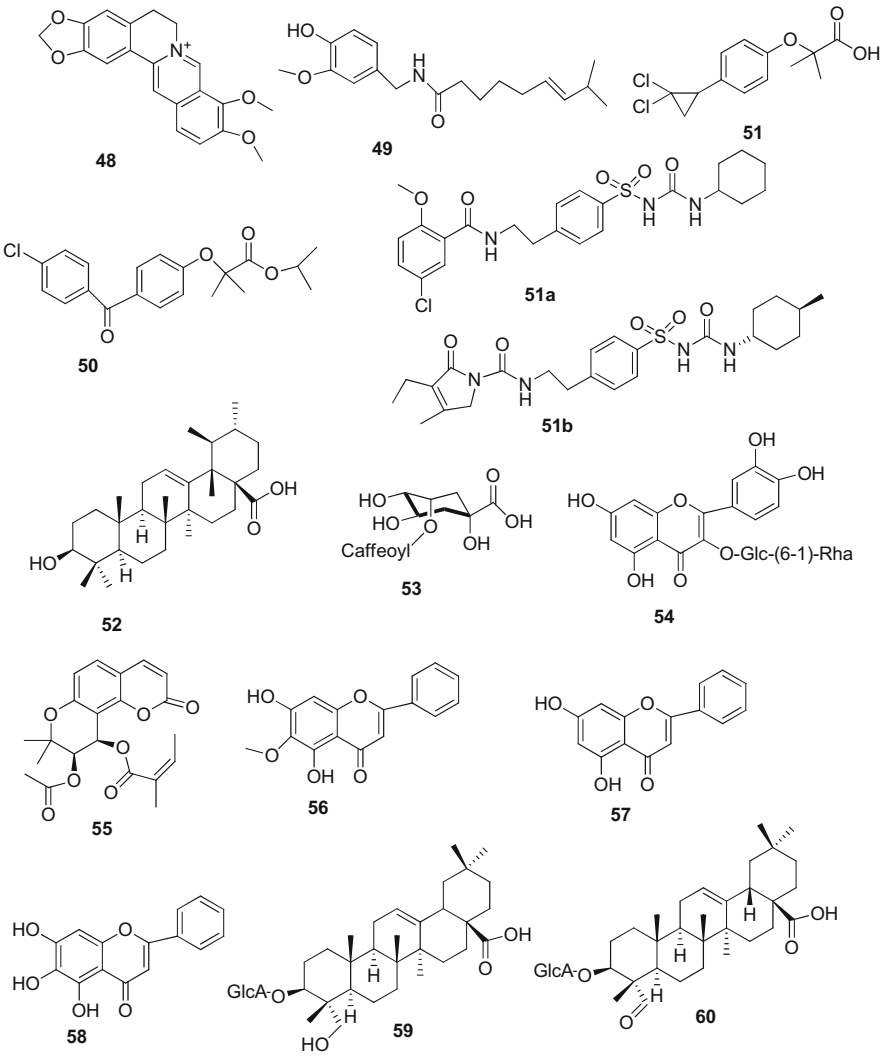

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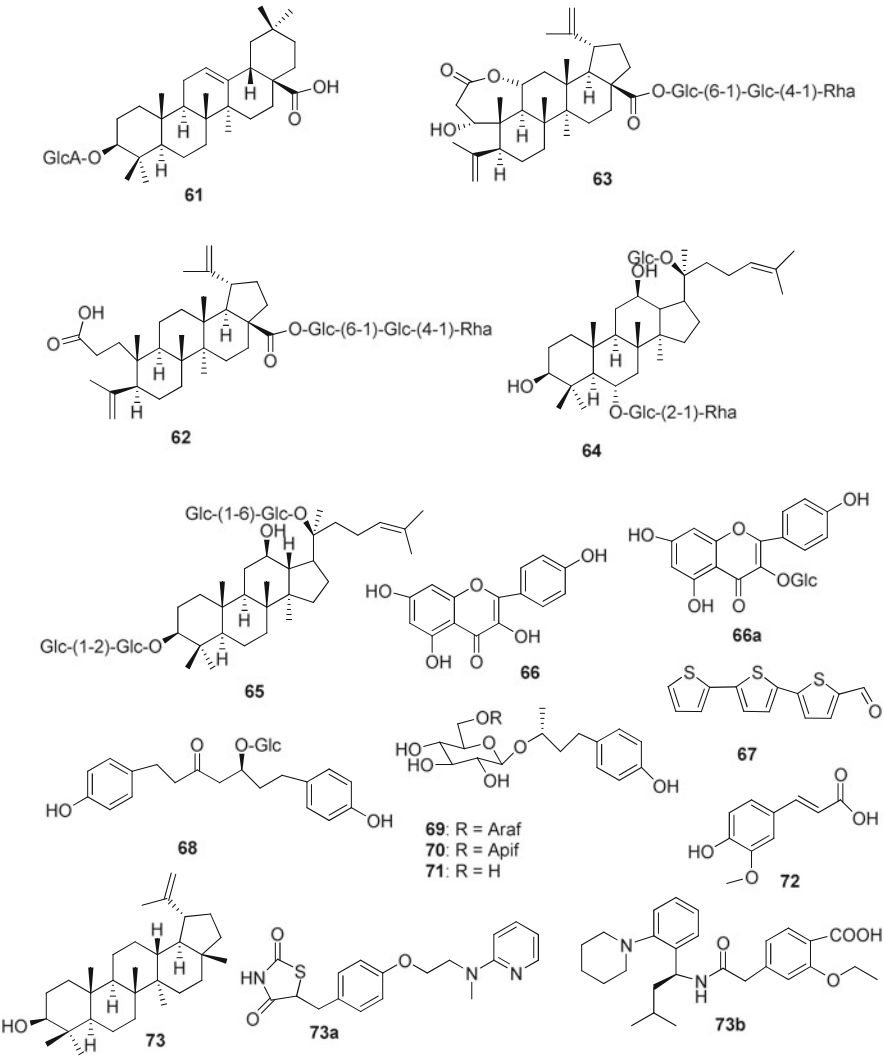

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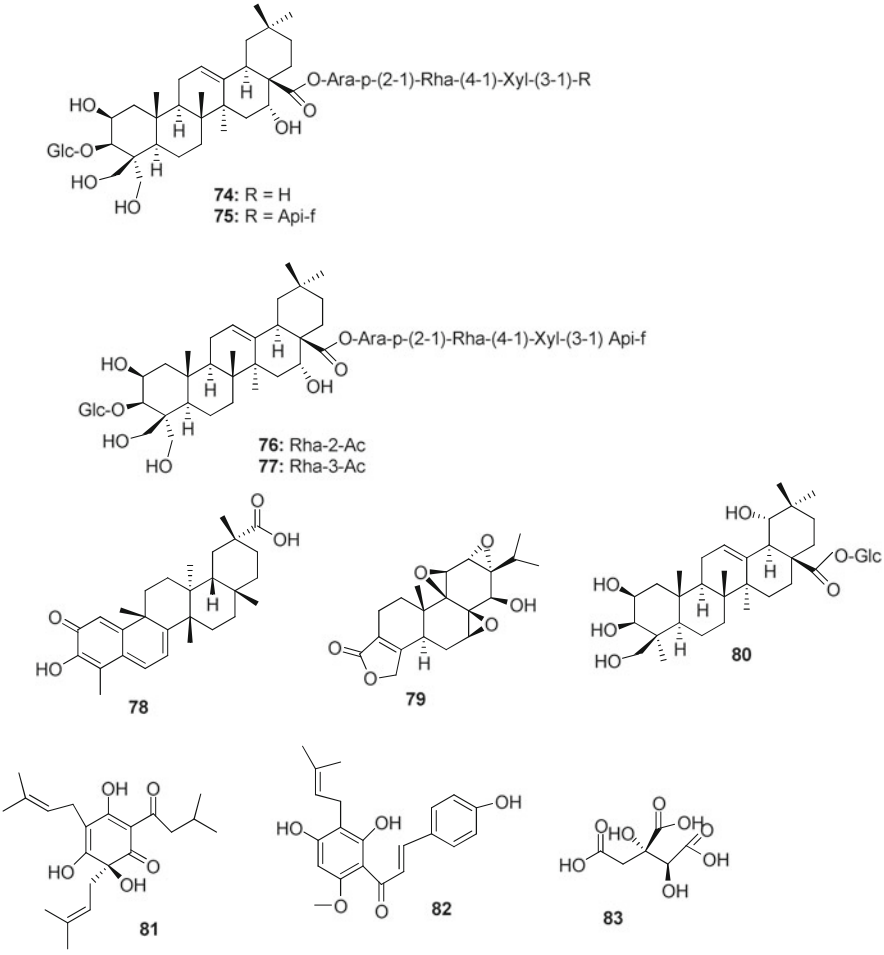

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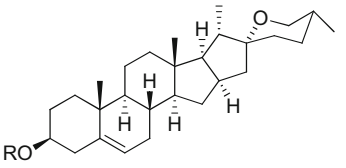
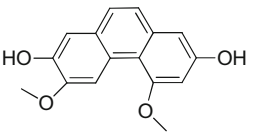


84: R = -Glc-(4-1)-Rha,-(2-1)-Rha
85: R = -Glc-(3-1)-Glc, -(2-1)-Rha
86: R = -Glc
87: R = -H
88: R = -Glc-(2-1)-Rha
89: R = -Glc



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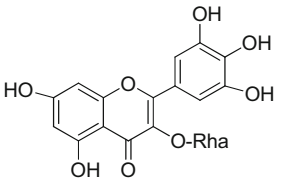

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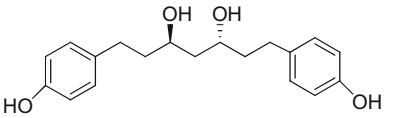

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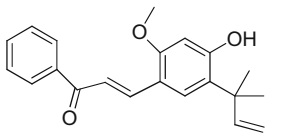

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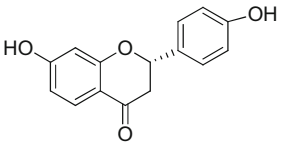

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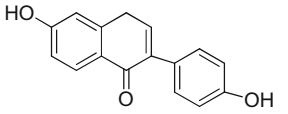

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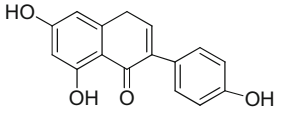

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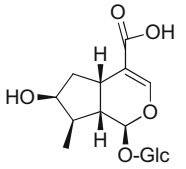

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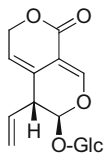

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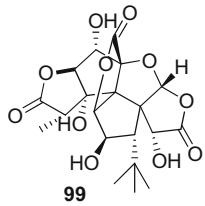

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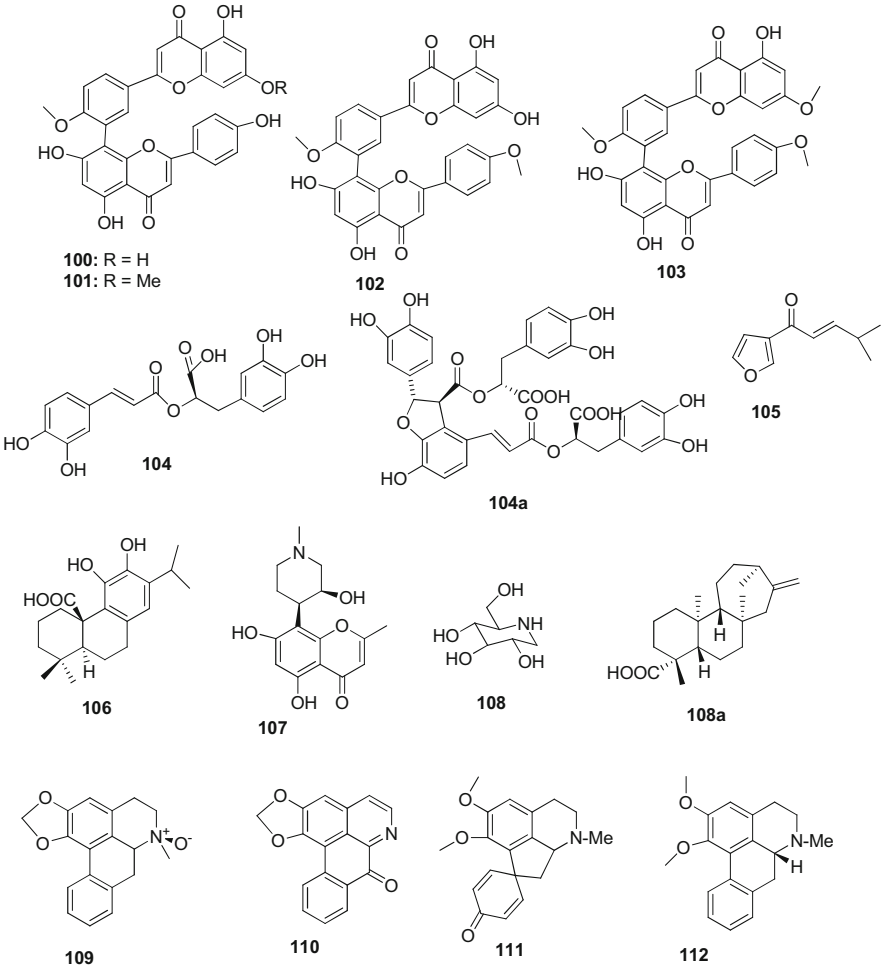

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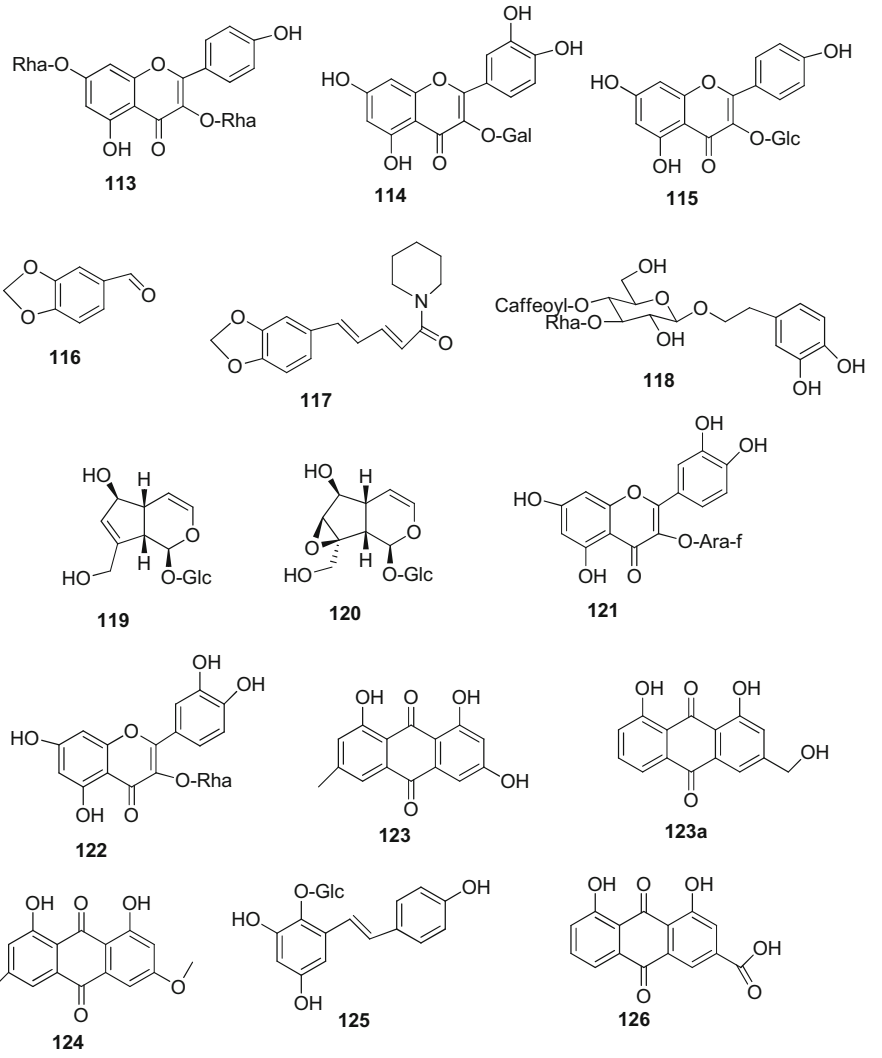

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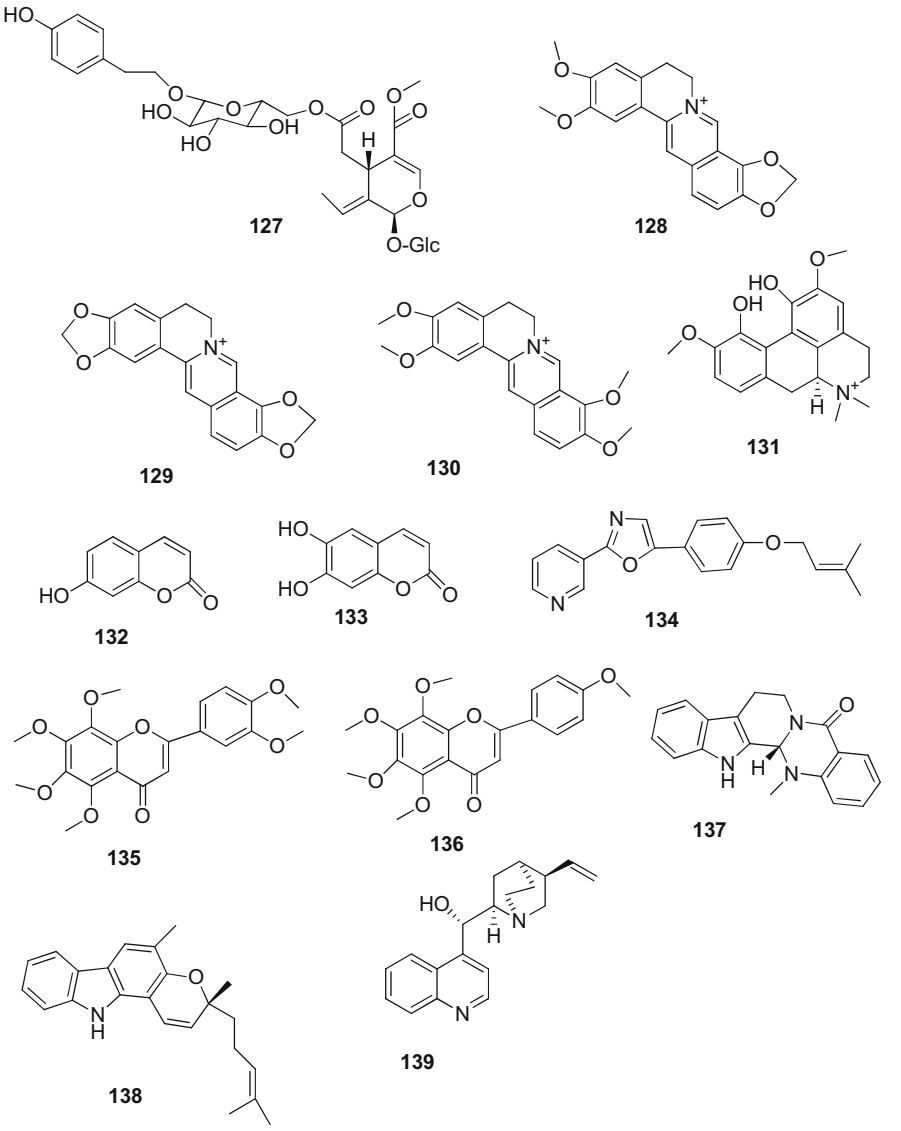

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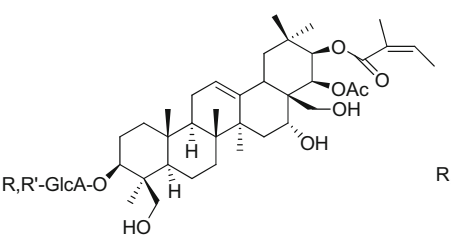
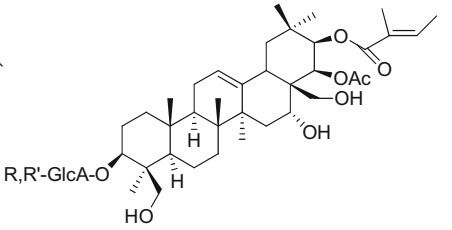
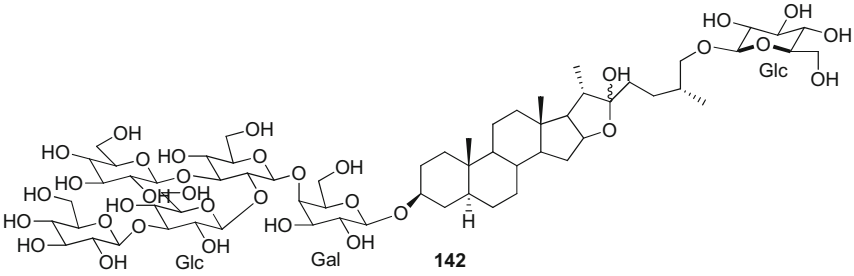


140: R = -(4-1)-Glc, R' = -(2-1)-Glc



141: R = -(4-1)-Glc, R' = -(2-1)-Xyl



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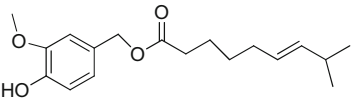

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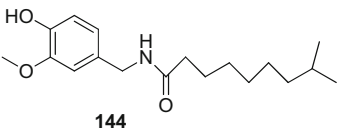

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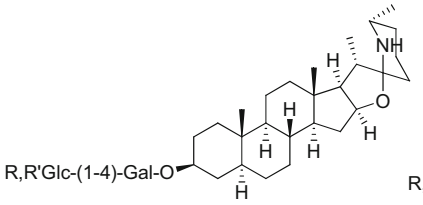
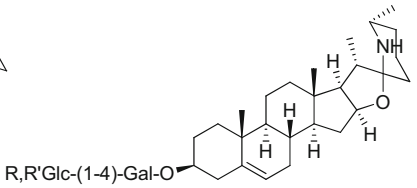
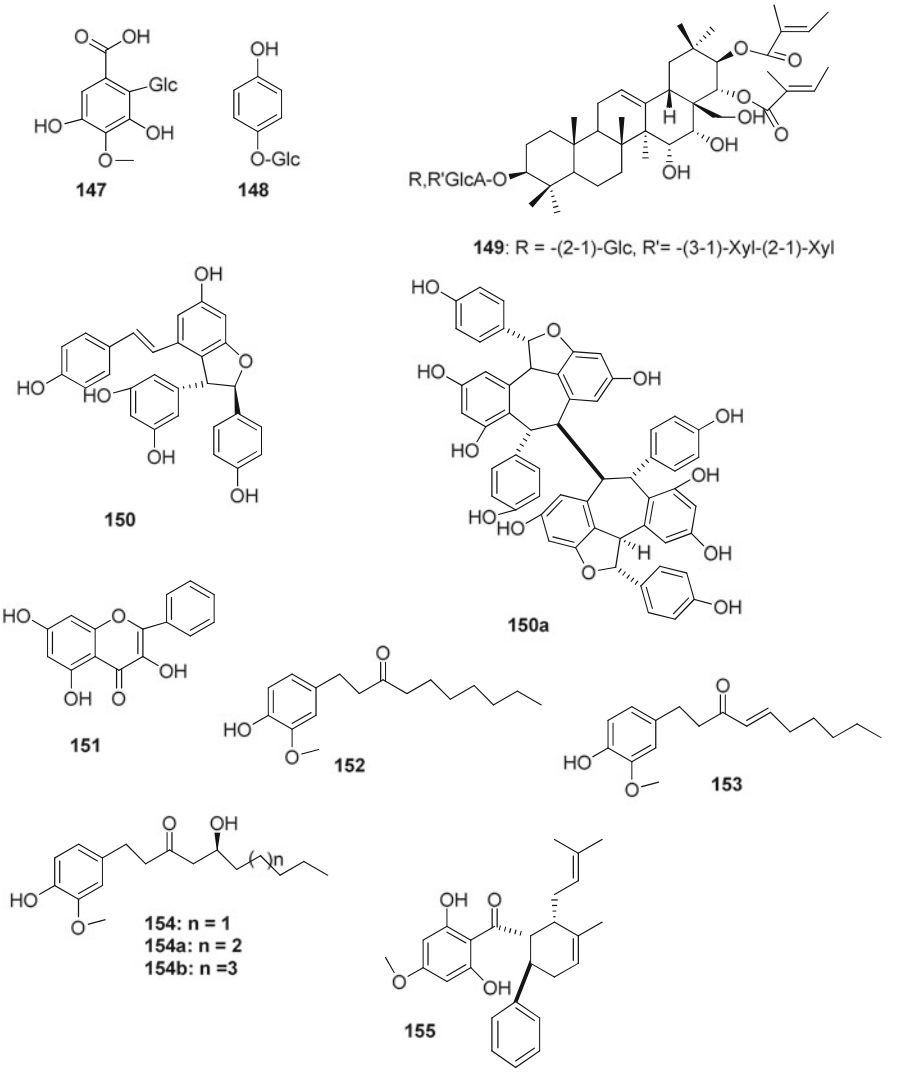


145: R = -(2-1)-Glc, R' = -(3-1)-Xyl



146: R =-(2-1)-Glc, R' = -(3-1)-Xyl

Fig. 4.1 (continued)



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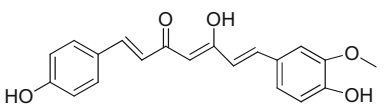

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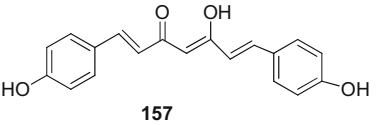

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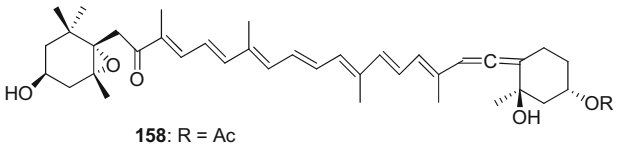
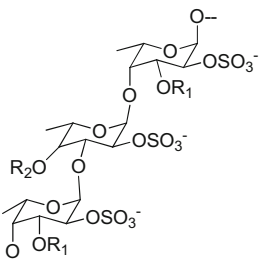
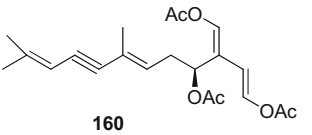


158: R = Ac
158a: R = H



159: R_1 = SO_3- or H, R_2 = SO_3- or H



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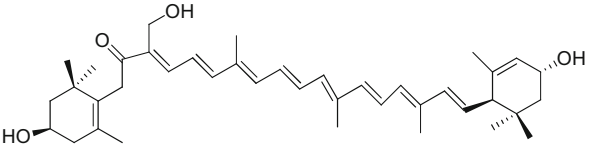

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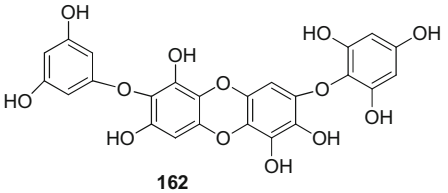

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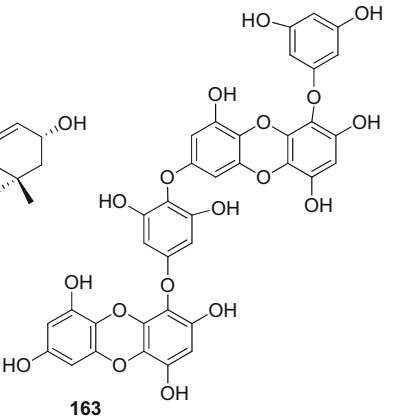

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Fig. 4.1 (continued)

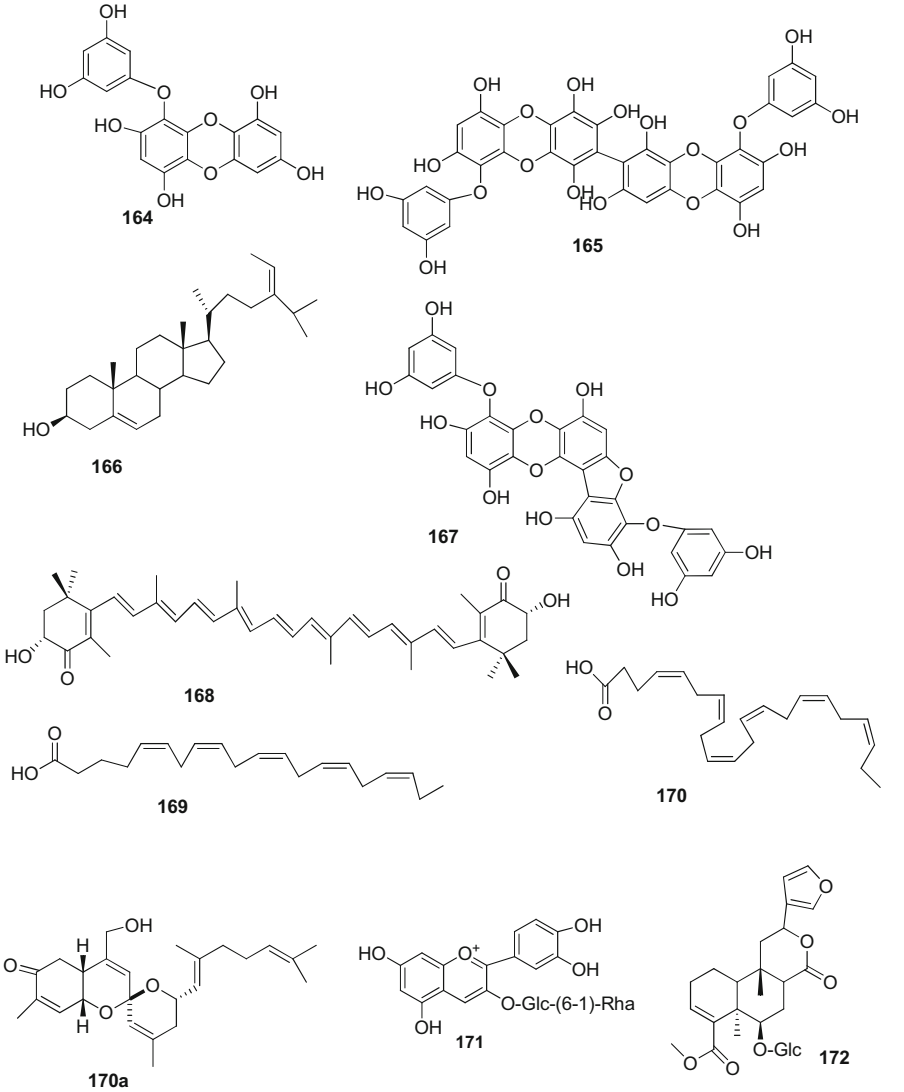
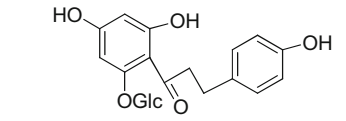


Fig. 4.1 (continued)



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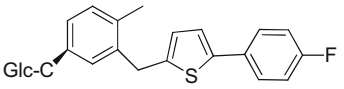

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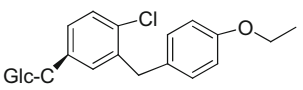

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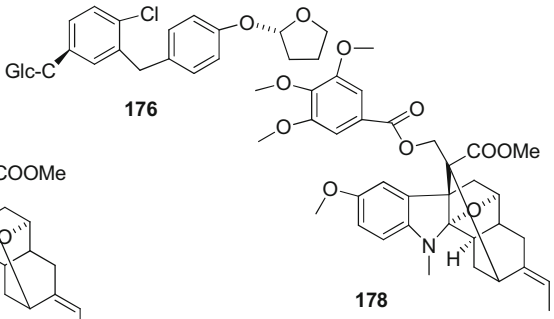

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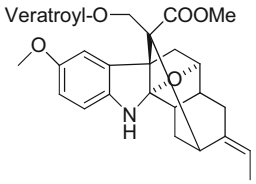
178



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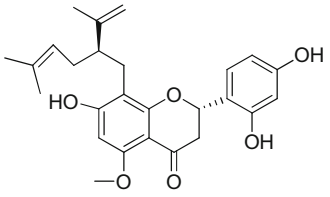

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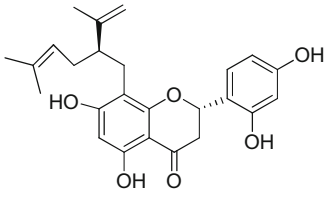

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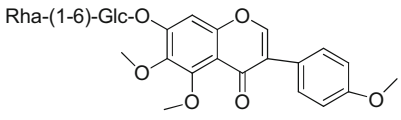

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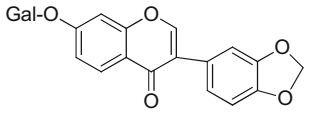
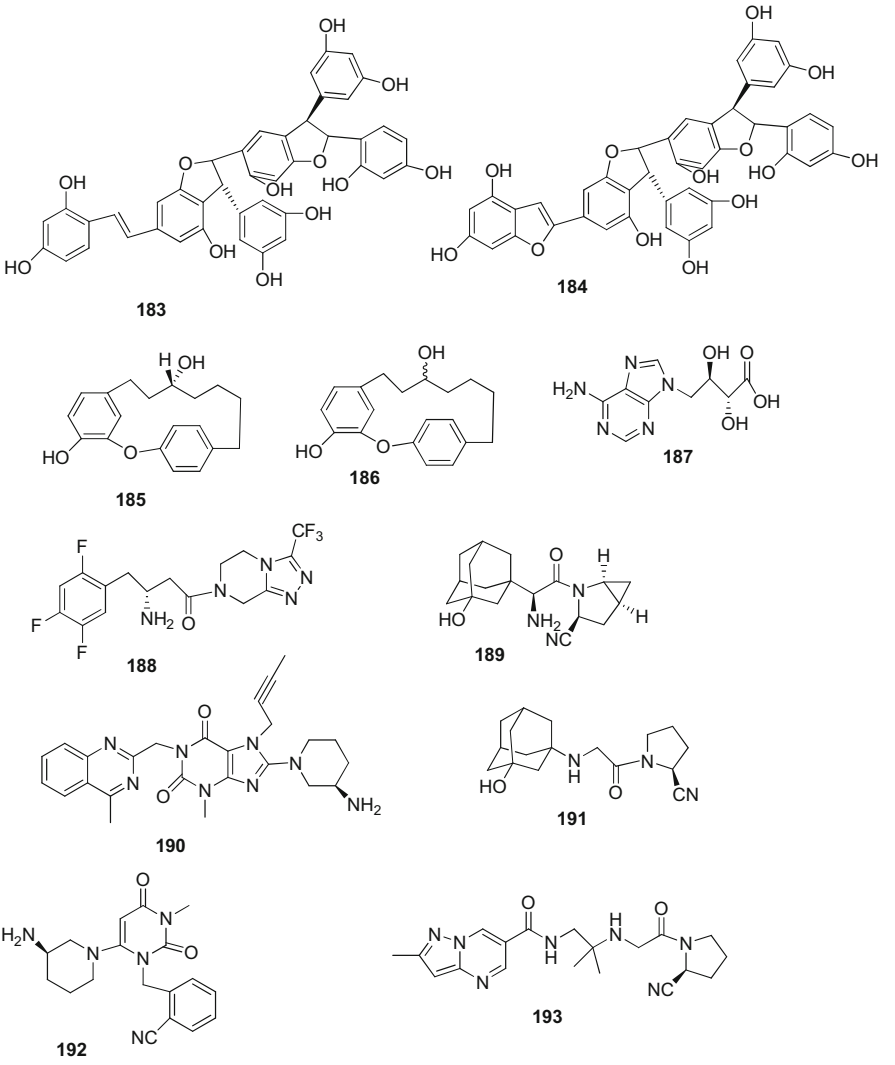


182

Fig. 4.1 (continued)



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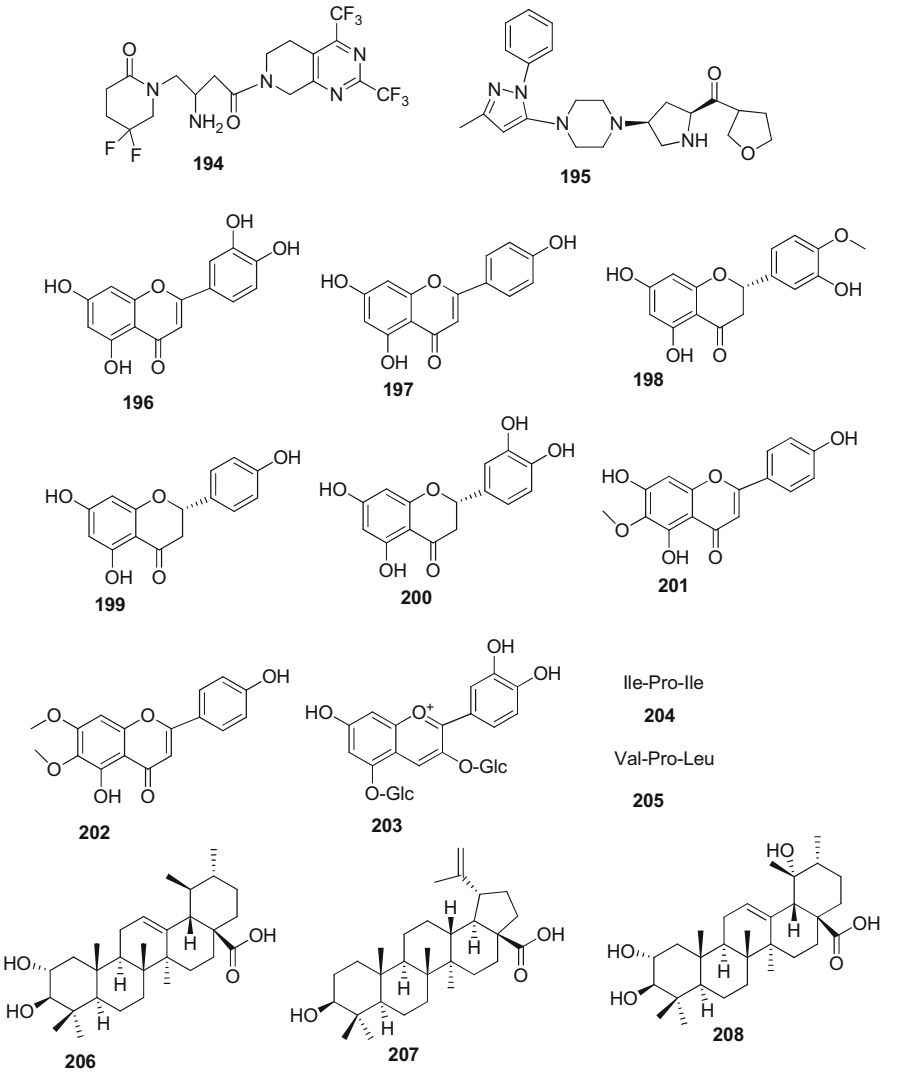
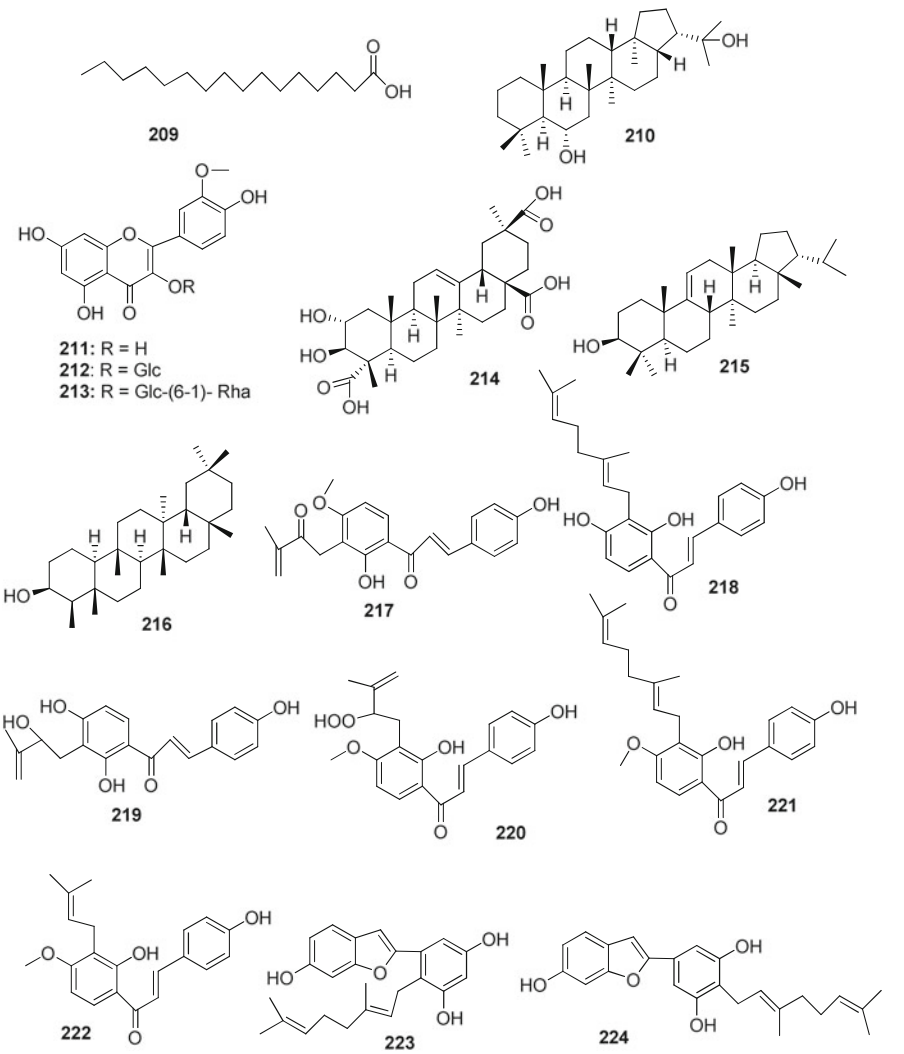


Fig. 4.1 (continued)



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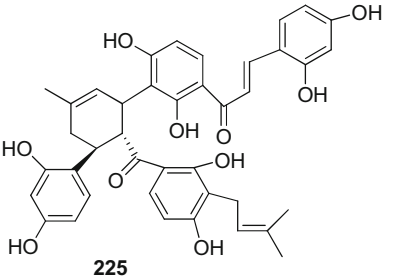

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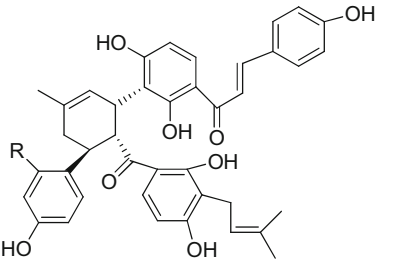
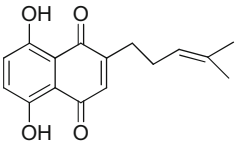


226: R = OH
227: R = H



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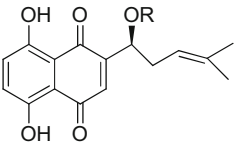
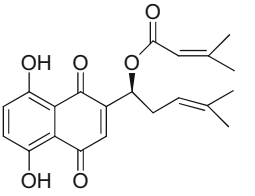


229: R = H
230: R = Ac



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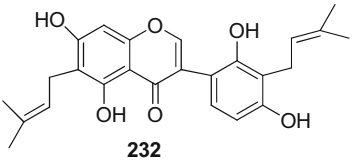

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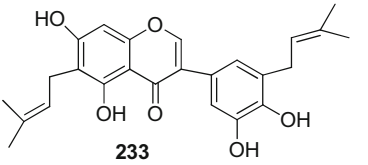

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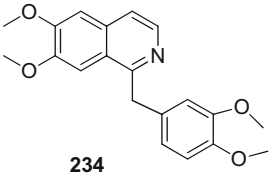

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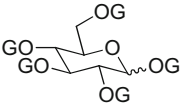
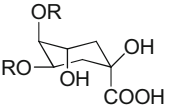
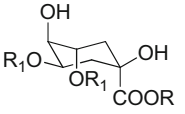


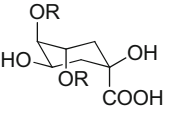
235: G = Galloyl



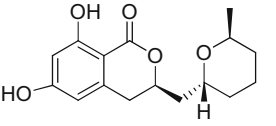
236: R = Caffeoyl



237: R = H, R_1 = Caffeoyl
238: R = Me, R_1 = Caffeoyl



239: R = Caffeoyl



240

Fig. 4.1 (continued)

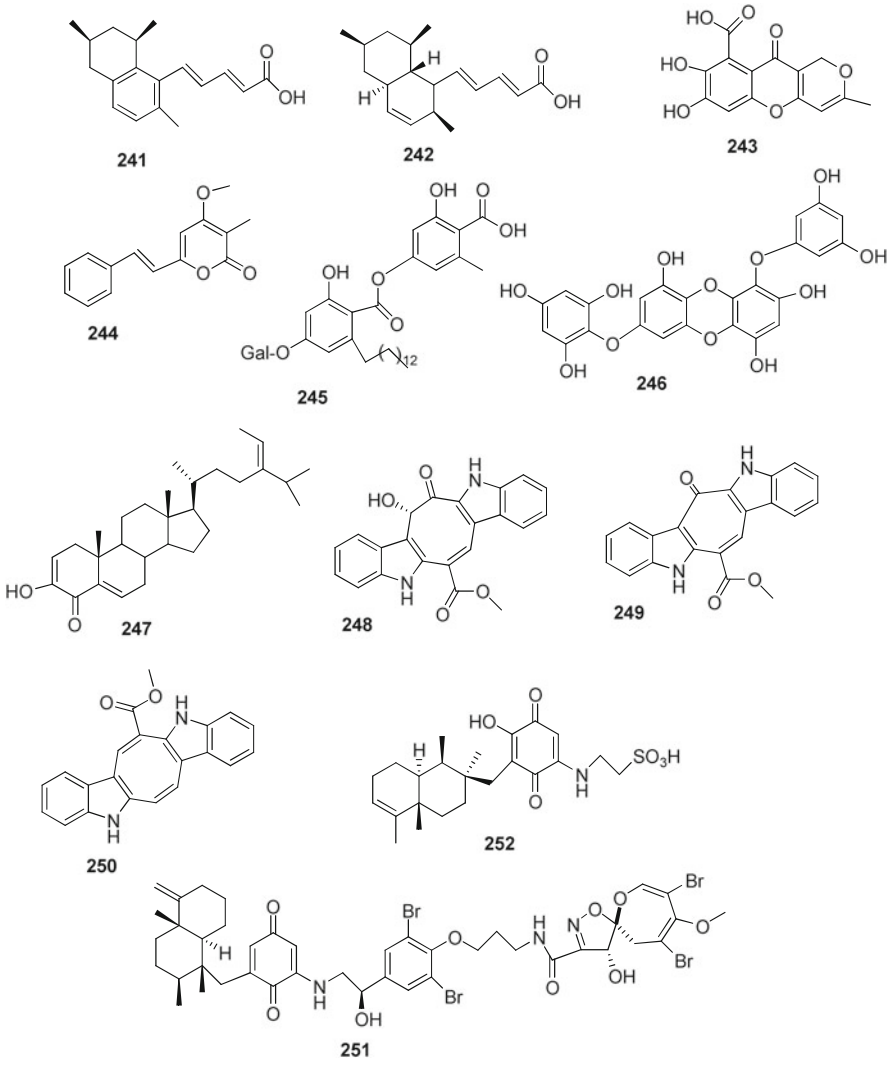


Fig. 4.1 (continued)

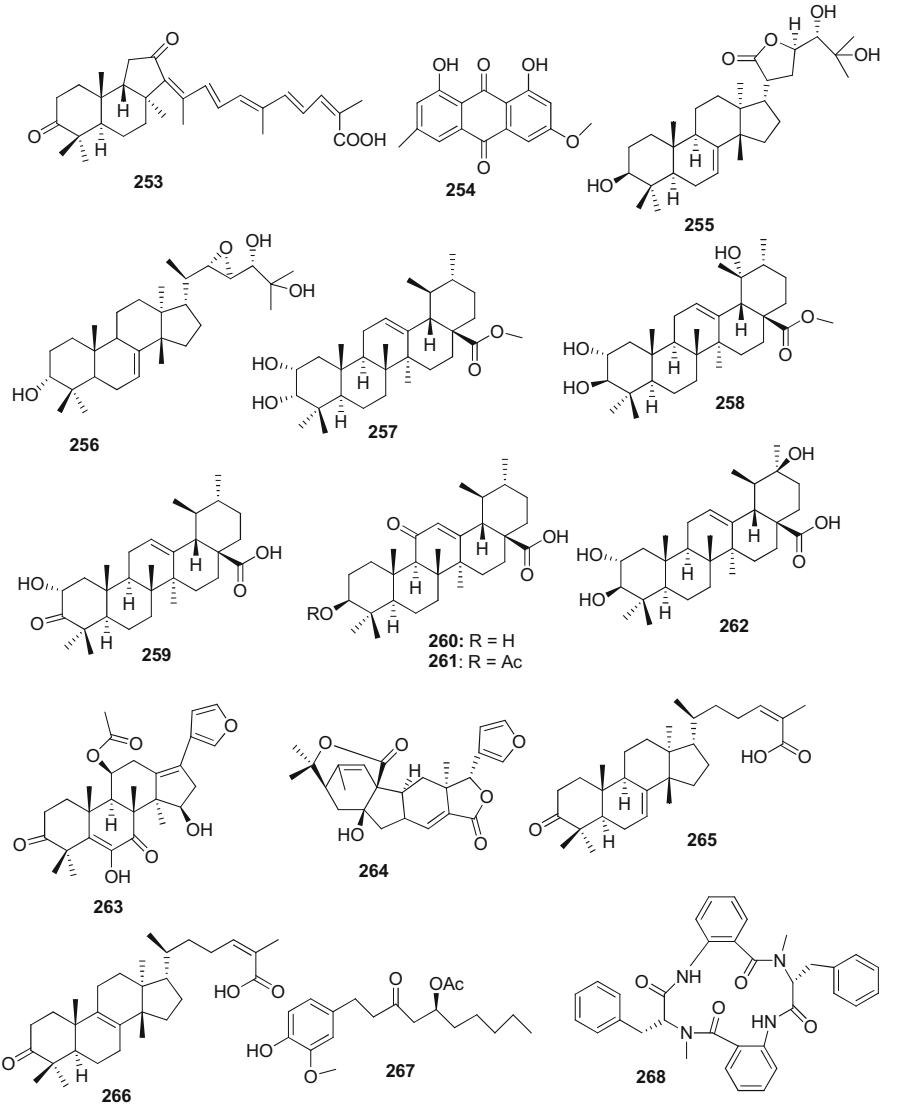
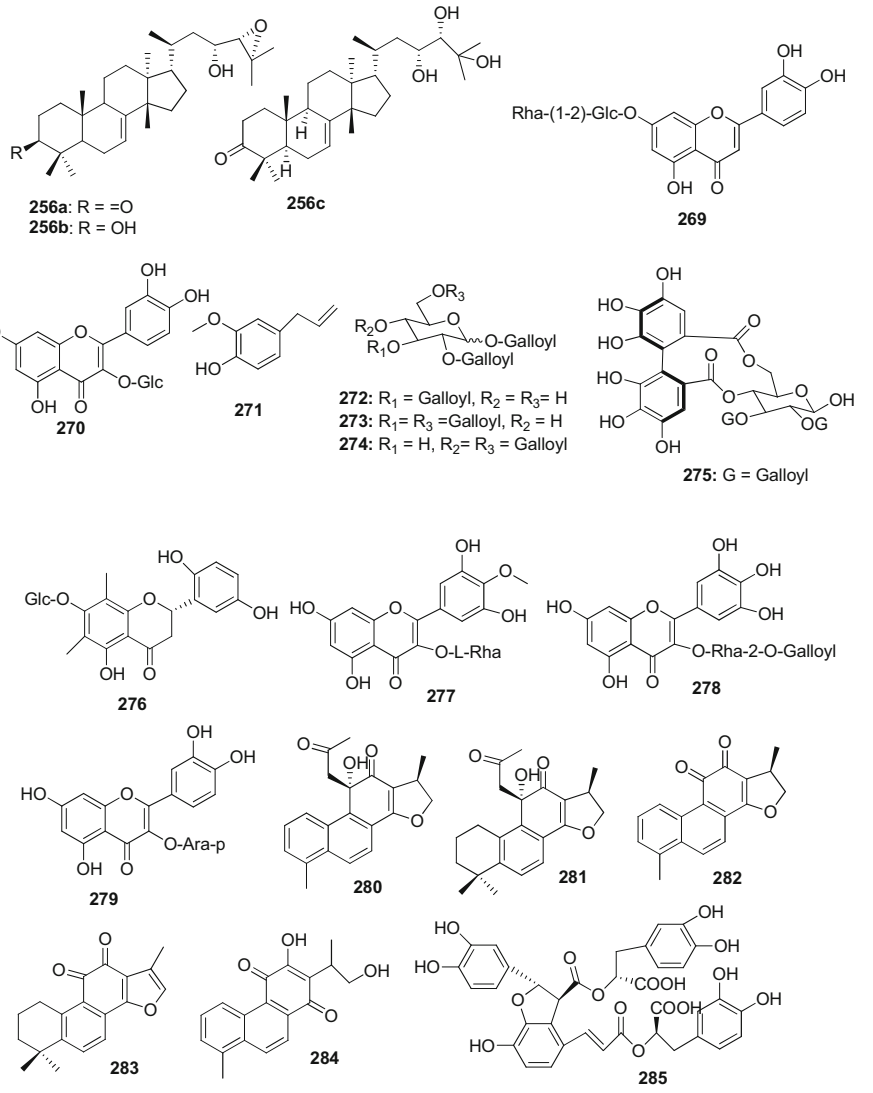


Fig. 4.1 (continued)



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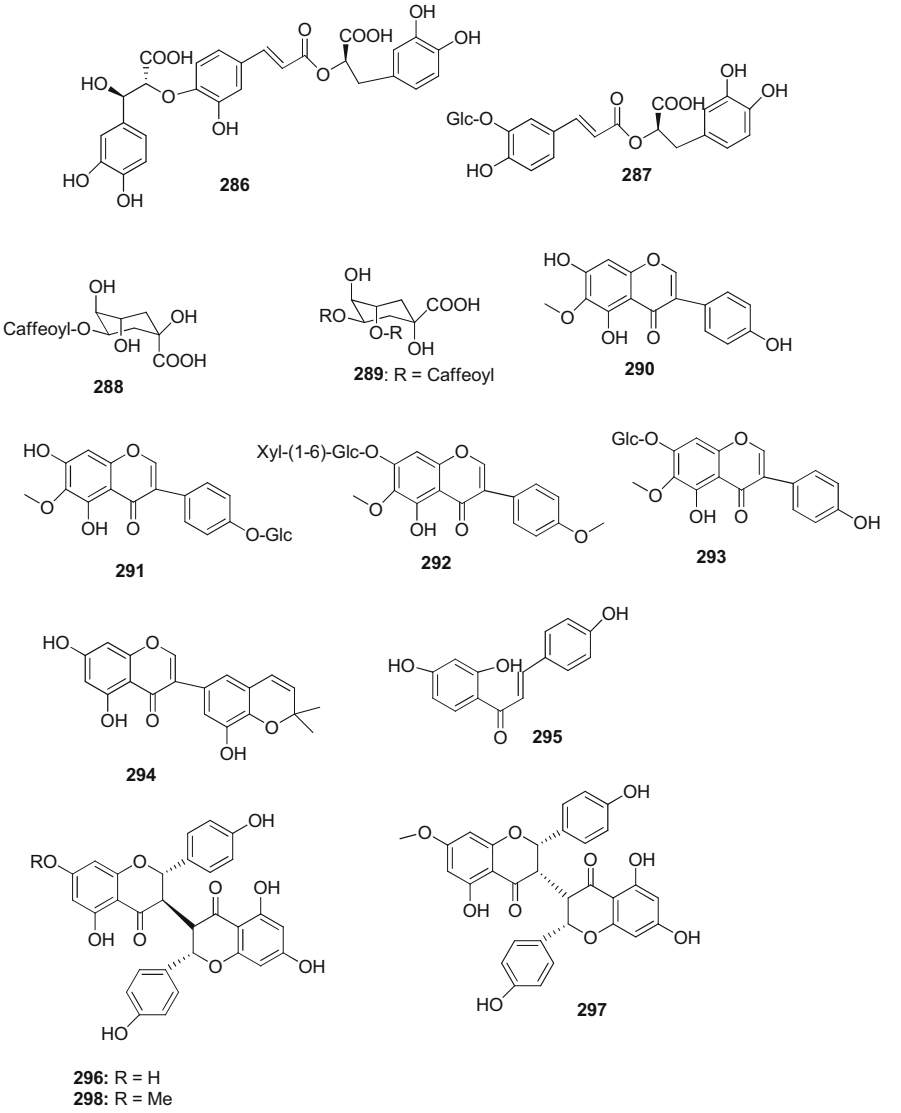
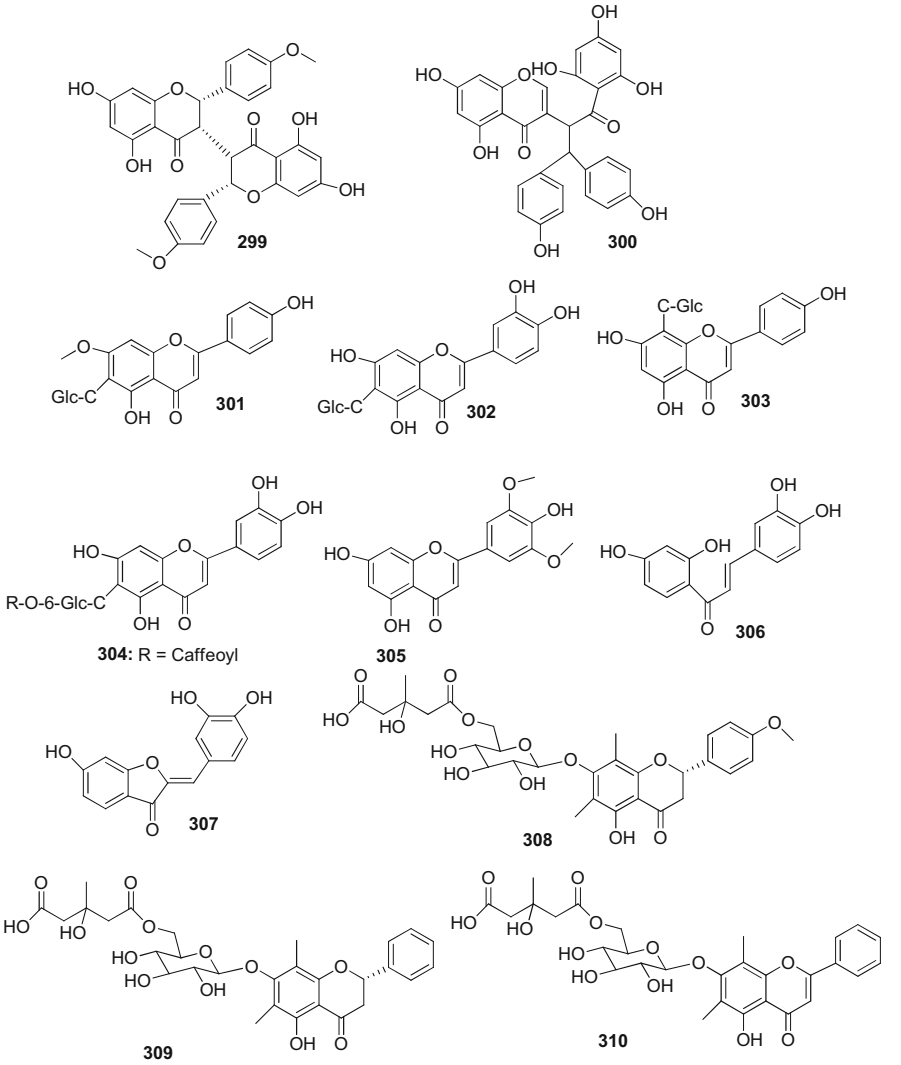


Fig. 4.1 (continued)



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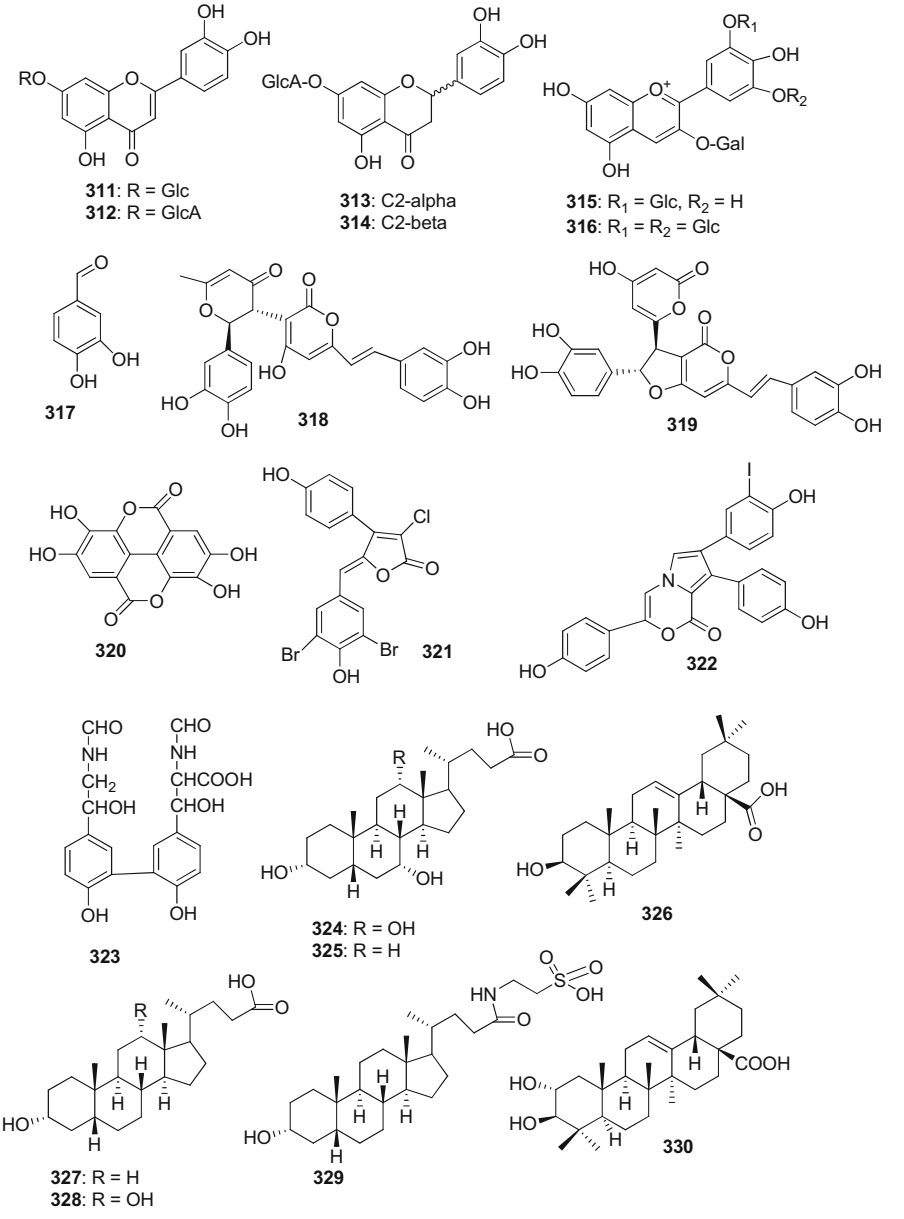

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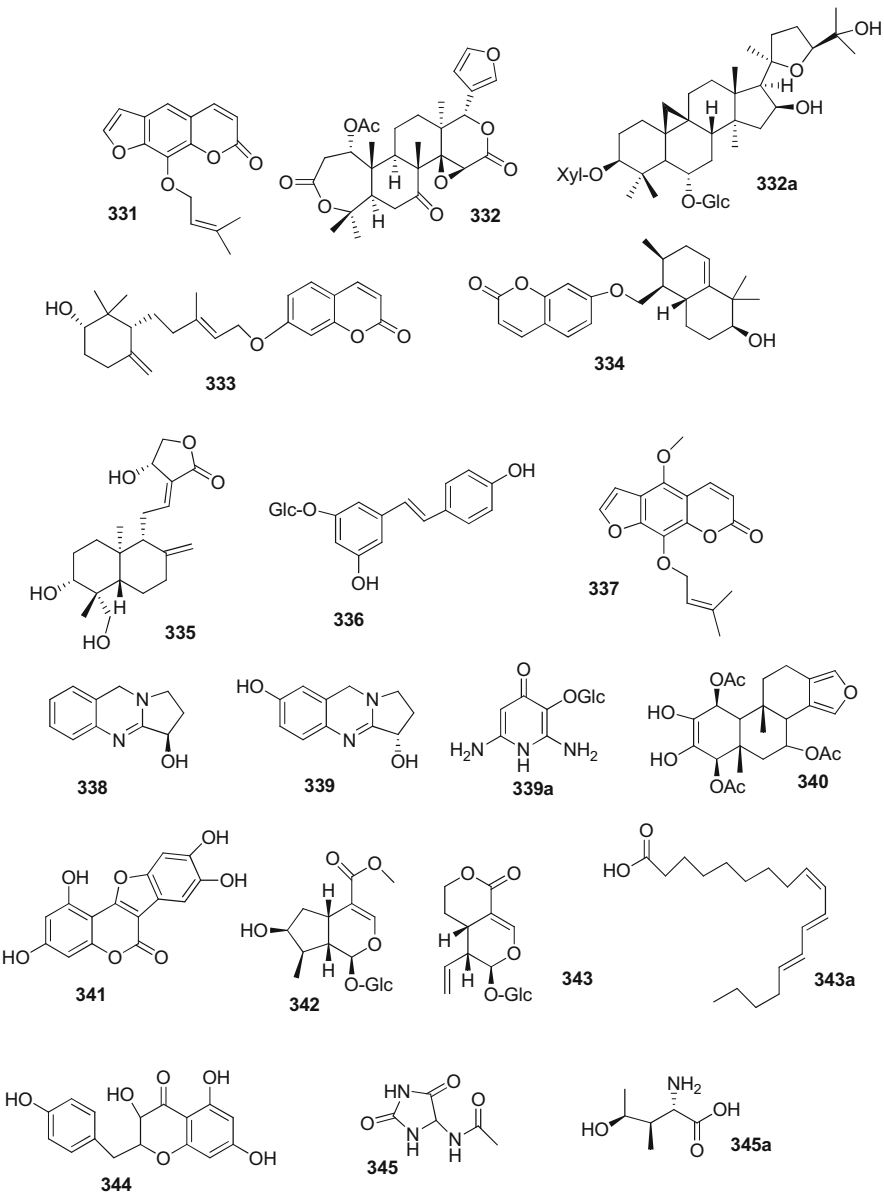
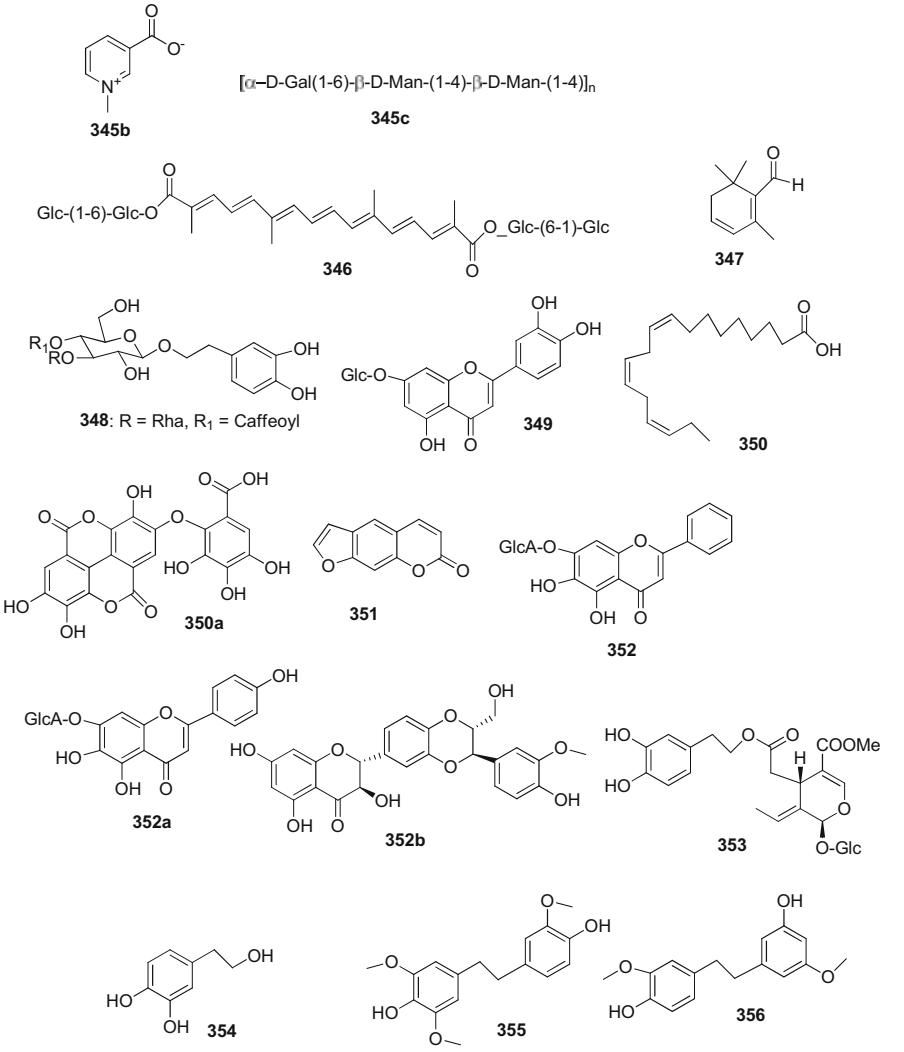


Fig. 4.1 (continued)



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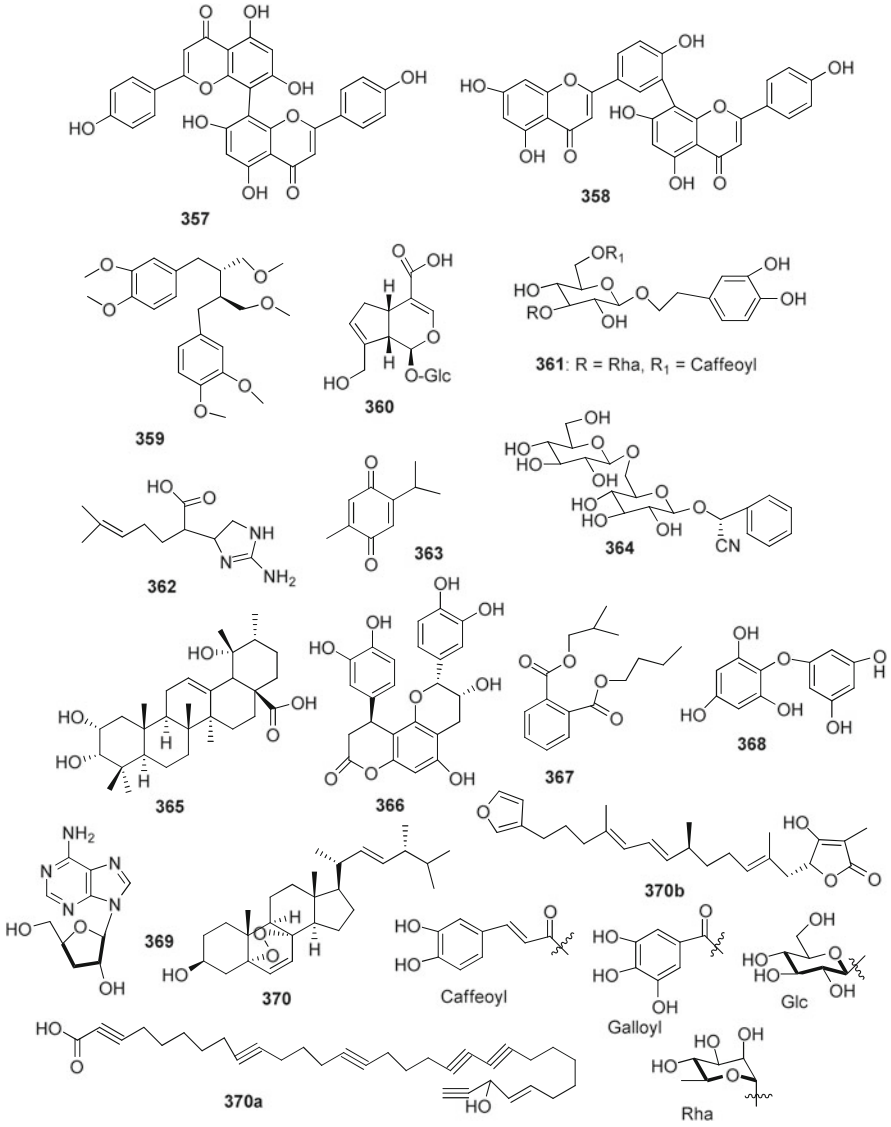

Fig. 4.1 (continued)

its rebound to 45% in 2010, then reduced to 13% in 2013, and increased again to 25% in 2015 and 33% in 2018 (Newman and Cragg 2020).

Among the existing 250,000–500,000 plant species, only a tiny proportion (about 5000 species) has been scientifically evaluated for bioactivities (Ngo et al. 2013; Payne et al. 1991). As per report of the International Union for Conservation of Nature and the World Wildlife Fund, about 50,000–80,000 flowering plants are being used for medicinal purpose worldwide. China and India have the highest numbers of medicinal plants used with 11,146 and 7500 species, respectively (Chen et al. 2016a). The WHO identified 21,000 medicinal plants from worldwide for evaluation of therapeutic potential, and out of them, 2500 species are of Indian origin, because of the location of India in a favorable climatic and geographical position for biodiversity (Modak et al. 2007). Therefore, a great proportion of untapped plants are remained to be explored in future research for identification of new natural products, which might offer huge potential information on their novel chemical structures and new types of biological actions related to new drug development. Recently introduced "multi-omics biotechnologies" are potential tools in the smart screening, robotic separation, and structural identification of bioactive metabolites and the proteins and genes involved in the biosynthesis of these metabolites. Moreover, these genomic, proteomic, transcriptomic, and metabolomic data analyses are greatly suitable for identification of plant species and microorganisms of therapeutic potential and their active metabolites by the use of instrumental facilities such as high-performance liquid chromatography, nuclear magnetic resonance spectroscopy, mass spectrometry, microfluidics, and computational algorithms. A recent report indicates that over 2,140,000 secondary metabolites from natural sources (plants, seaweeds, land and marine microorganisms, and marine animals) have been investigated and among them, over 35,000 are terpenoids and steroids (McMurry 2015). For example, the transcriptomic data of *Catharanthus roseus* helped us to find out the enzyme, iridoid synthase, responsible for conversion of linear monoterpene 10-oxo-geranial into bicyclic iridoids in medicinal plants by reduction and subsequent cyclization via a DA cycloaddition or a Michael addition (Geu-Flores et al. 2012). The genome analysis of medicinal plant, *Salvia miltiorrhiza* revealed the presence of 40 genes responsible for terpenoid biosynthesis, and out of them, 27 were novel, and 20 genes were involved in the biosynthesis of bioactive diterpenoids tanshinones (Ma et al. 2012). We have to pay our interest on herbal genomics and transcriptomics for the search of genes and enzymes that are used by medicinal plants and microorganisms for the synthesis of bioactive secondary metabolites and to use these genes and enzymes in biotechnical processes, such as in tissue culture, micropropagation, synthetic seed technology and molecular (SSRs) marker-based approaches for genome analysis, and plant breeding study to improve the yield and potency of medicinal plants as well as for large-scale production of these bioactive natural metabolites for their extensive clinical trials and commercial application (Chen et al. 2015, 2016a; Hao and Xiao 2015; Pandita et al. 2021; Sahu et al. 2014). Therefore, most of the pharmaceutical industries and research organizations related to drug

discovery have to rethink on their strategy for development of new drugs from untapped natural resources (Ngo et al. 2013; Zhu et al. 2012).

4.3 Factors Affecting the Composition and Contents of Phytochemicals in Processed Vegetative Foods

Phytochemicals are the important bioactive compounds of plant foods, such as fruits, vegetables, whole grains, and beverages, and are well recognized for their antioxidant, anti-inflammatory, and nutraceutical potentials, and their dietary consumption as plant foods is positively associated with health benefits, particularly in preventing the risks of a number of chronic diseases including obesity, diabetes, cardiovascular diseases, and cancers. Several studies demonstrate that the levels and composition of phytochemicals, such as phenolics (including flavonoids, catechins, anthocyanins, tannins and phenolic acids), terpenoids, carotenoids, saponins, alkaloids, and glucosinolates, depend on many factors, such as cultivar types, propagation types, environmental and agronomic conditions, harvest and food processing operations, and storage factors. Adequate knowledge on these areas might be useful to take suitable strategies in different stages of cultivation, harvesting, and post-storage of these dietary crops by the food producers to get maximum yields of better quality of fruits, vegetables, and other crops having high concentrations of bioactive phytochemicals (Tiwari and Cummins 2013; Li et al. 2012a).

4.3.1 Cultivar Effect

Fruits and vegetable growers need to select the cultivars or genotypes of a crop with high phenolic and carotenoids content. About 70–90% of the carotenoids consumed by humans are available from dietary fruits and vegetables. However, most of the fruits and vegetable growers prefer to cultivate a cultivar that provides high yield and large size of fruits and vegetables as per consumer's demand rather than considering the high quality of these fruits and vegetables in terms of health-benefit potential and concentration levels of bioactive phytochemicals. For instance, blueberry (*Vaccinium* spp.) fruits have health benefit effects due to presence of high content of polyphenolic compounds, particularly anthocyanins, flavonoids, chlorogenic acids, and other compounds, cellulose (about 3.5%), pectin (about 0.7%), and dietary fibers (about 1.5%), which have nutritional value. In New Zealand, two cultivars of blueberry, *Vaccinium corymbosum* and *V. virgatum*, are commercially cultivated. The highbush blueberry, *V. corymbosum*, is more acceptable to the consumers compared to rabbiteye blueberry *V. virgatum*, because of less seediness and better fruit size, although it has lower anthocyanins content (18–249 mg/100 g of fw) compared to rabbiteye seedy variety (12.7–410 mg/100 g of fw) (Scalzo et al. 2015). The delicious strawberry fruits (*Fragaria* × *ananassa* Duch) are consumed both as fresh and processed, because of the presence of health benefit polyphenolic compounds, anthocyanins, ellagitannins, flavonols, and polymeric flavan-3-ols. The

identification and quantification of the phenolic compounds in 27 cultivars of strawberry grown in Norway and harvested in 2009 revealed that total phenolic compounds content varied among the cultivars, from 57 to 133 mg/100 g of fw. Among the polyphenolic compounds, anthocyanins were most abundant (8.5–65.9 mg/100 g of fw), followed by flavan-3-ols (11–45 mg/100 g of fw), and ellagitannins (7.7–18.2 mg/100 g of fw). Among the common cultivars, Blink, Korona, Polka and Senga Sengana, among them, Senga Sengana is preferred for processing due to its low anthocyanins content (27.4 mg/100 g of fw), and Korona is preferred for fresh consumption due to high anthocyanins content (49.1 mg/100 g of fw) (Aaby et al. 2005, 2012). The contents of a variety of polyphenols (about 48) and triterpenes (mainly 3) at the ripening stage of three cranberry cultivars, Pilgrim, Stevens, and Ben Lear, grown in Poland are found different, although these polyphenols and triterpenes are identified in all these genotypes. The cultivar Stevens has highest concentrations of bioactive phenolic acids and antioxidant capacity compared to other tested cultivars (Oszmianski et al. 2018). Genotype (cultivar) variation in stone fruits, nectarines (*Prunus persica*), peaches (*Prunus persica vulgaris*), and plums (*Prunus salicina*) also reflects the variation of composition and contents of phenolic compounds, carotenoids, and vitamin C. A comparative study to the chemical composition of the stone fruits, from five cultivars, each of white-flesh nectarines, yellow-flesh nectarines, white-flesh peaches, and yellow-flesh peaches and plums, grown in California, revealed the ranges of total phenolics (in mg/100 g of fw) 14–102, 18–25. 28–111, 21–61, and 42–109; total carotenoids (mg/100 g of fw) 7–14, 80–186, 7–20, 71–210, and 70–260; and vitamin C (mg/100 g of fw) 5–14, 6–8, 6–9, 4–13, and 3–10, respectively. Major phenolic compounds in these fruits are hydroxycinnamic acids, flavan-3-ols, flavonols, and anthocyanins. In nectarines and peaches, both hydroxycinnamic acids and flavan-3-ols are strongly correlated with antioxidant activity of the fruits, whereas in case of plums, only flavan-3-ols are correlated to the antioxidant activity of fruits (Gil et al. 2002). A study on the phytochemicals levels and composition in the maturity stage of mulberry fruits in four cultivated mulberry cultivars, *Morus alba*, *M. laevigata*, *M. macroura*, and *M. nigra*, which are grown in Pakistan, reveals that the total phenolic content is highest in *M. nigra* (395–2287 mg GAE (gallic acid equivalent)/100 g of dw), while it is lowest in *M. laevigata* (201–1803 mg GAE/100 g of dw), whereas the total flavonoid content is highest in *M. nigra* (245–1021 mg catechin equivalent (CE)/100 g of dw), and it is lowest in *M. macroura* (145–249 mg CE/100 g of dw). Among the identified phenolic acids, p-coumaric acid (**19**) and vanillic acid (**20**) are major constituents in *M. nigra* and *M. laevigata*, while p-hydroxybenzoic acid and chlorogenic acid (**21**) are major phenolic acids in *M. alba* and *M. macroura*. Among the identified flavonoids, the content of myricetin (**22**) is high in *M. alba* (88 mg/100 g of dw) and the content of quercetin (**23**) is high in *M. laevigata* (145 mg/100 g of dw). It indicates that *M. nigra* cultivar fruits are rich in antioxidant phytochemicals (Mahmood et al. 2012).

A study on the contents and composition of phytochemicals in 20 cultivars of tomato (*Solanum lycopersicum* syn *Lycopersicon esculentum*) reveals that the levels of major phytochemicals, carotenoids (lycopene **24**, β-carotene **25**, all-*trans*-lutein

26, and their 22-*cis*-isomers) and phenolic compounds and their antioxidant activity are dependent on genetic background and maturity in the harvest stage (Li et al. 2012b). Among the two tomato cultivars, 'supersweet' cherry tomato and conventional 'counter' round tomato grown in a greenhouse, the cherry tomato has high content of lycopene (5.5–8.3 mg/100 g of fw) compared to round type (4.9–5.8 mg/100 g of fw), and high concentration is observed in autumn season (Krumbein et al. 2006).

4.3.2 Propagation Effect

The composition of phytochemicals, particularly phenolic compounds contents in berry fruits, depends on the propagation process of the berry plant, such as on seed germination process or clonal plantation through stem or rhizome cutting or in vitro microtissue culture process. Three varieties of blueberry crops, high-bush *Vaccinium corymbosum*, low-bush *V. angustifolium*, and rabbiteye *V. ashe* are commercially cultivated in many countries. Most of the nurseries or orchard farms prefer stem cutting (SC) and tissue culture (TC) process for propagation of blueberry plants rather than the conventional seed germination process. It is observed that in vitro TC-derived high bush and low bush blueberry plants grow faster with more shoots but with less flowers and smaller berries than SC-derived plants, while the berries from TC propagated plants have higher levels of polyphenols, flavonoids, and anthocyanins than that in the fruits from SC plants. Similar trends are also found in micro-propagated strawberry plants (Debnath and Goyali 2020).

4.3.3 Effects of Environmental Factors

Environmental factors, such as geographic location, soil type, soil nutritional status, temperature, precipitation, and sunlight, influence the concentrations and composition of phytochemicals in vegetable crops (Lumpkin 2005). Each vegetable crop requires a specific environmental setup that provides the crop plants to reach better growth and high concentrations of health-promoting phytochemicals. It has been observed that faster growth rate of crop plants reduces the concentrations of polyphenols and vitamins in crops by dilution effect (Davis et al. 2004). Soil-type and appropriate nutrient supply enhance the concentrations of antioxidant phytochemicals in vegetable crops. Available evidence demonstrates that muck soil rich in decomposed organic matters and nitrogen content is suitable for the growth of root crops, onions, carrots, radishes, lettuces, celery, etc. Cultivation of onions in raised beds (zone tillage) provides better size and yield of onions compared to conventional flat beds cultivation (Swanton et al. 2004). Soil moisture content also influences the concentrations of phytochemicals in vegetable crops. The bioactive polyacetylenes, falcarinol (**27**) and falcarindiol (**28**), present in carrots (*Daucus carota*) improve insulin stimulated glucose uptake in human adipocytes and myotubes and have antidiabetic property. In water stress conditions such as

insufficient water or excess soil moisture in carrot (cv 'Orlando Gold') grown in the green house reduce the concentrations of eight polyacetylenes including three known ones, falcarinol, falcarindiol, and falcarindiol-3-acetate (**29**) by about 30%, 37%, and 46%, respectively (Lund and White 1990). Tomato is the second largest group of vegetable crops cultivated in the world. It is rich in carotenoids (lycopene (**24**) of about 90% and β-carotene (**25**) of 6–8%), tocopherols, vitamin C, potassium, and iron. Consumption of tomatoes in diet significantly reduces the risk of atherosclerosis, cardiovascular diseases, and some types of cancer (Olson 1986). Lycopene content in tomatoes depends on water supply and temperature. The less-water supply and moderate temperature (12–32°C) favor high lycopene content. For this reason, higher lycopene content is observed in tomatoes harvested in greenhouse (83 mg/kg of fw) than in field-grown tomatoes (59.2 mg/kg of fw) at every harvesting time (Brandt et al. 2003). Another study reported that a temperature range (15–24°C) showed maximum concentration of lycopene, after which, lycopene biosynthesis was reduced sharply and completely inhibited at 32°C. For this reason, winter season is the best time for tomato cultivation in open fields (Krumbein et al. 2006). Agronomic practice of crop plants in extreme environmental stress situation influences the levels of phytochemicals in many vegetable crops. For example, application of rich sulfur fertilization (150 kg/ha) in the cultivation of eight broccoli cultivars in late spring season increases the total phenolic content (flavonoid content (about 3-fold) followed by total sinapic and feruloyl acid derivatives and total caffeoylquinic acid derivatives) and vitamin C content compared to those grown in poor sulfur fertilization (15 kg/ha) and conventional early winter season. Moreover, five commercially grown cultivars produced higher amounts of phenolic compounds and vitamin C than three experimental ones (Vallejo et al. 2003). Sowing season of agronomic practices has an impact on the levels of phytochemicals in crops. In Northwestern Spain, cabbages (*Brassica oleracea*) planted during the fall/winter season had 40% less of total glucosinolate content (13 μM/g of dw) than the same varieties planted during the spring/summer season (glucosinolate content, 22 μM/g of dw) (Cartea et al. 2008). Possibly higher day/night temperature (30/15°C) regime in spring favors healthy growth of sprouts compared to the lower fall day/night temperature (22/12°C) regime which improves glucosinolate levels in both cabbage and broccoli (*Brassica oleracea* var. *italica*). High day temperature-induced stress increases the expression levels of phase 2 chemoprotective enzymes (Pereira et al. 2002). Soil nutrients have a significant role in the concentrations of glucosinolates in cabbage. Low nitrogen and high sulfur applications during the growth of cabbage cultivars improve the total glucosinolate and glucobrassicin contents in cabbage (Rosen et al. 2005).

Climate condition in harvest season of fruits influences the concentrations of phytochemicals in fruits. Black chokeberry (*Aronia melanocarpa*) cultivars are cultivated in large scale in North America, Canada, and European countries because of high nutritional benefits of its fruits. The fruits are rich in anthocyanins (mainly cyanidin glycosides), proanthocyanidins (mainly oligomers and polymers of (-)-epicatechin linked by B-and A-type bonds), flavonoids and phenolic acids, vitamins, carbohydrates, PUFA, dietary fibers, and minerals, and fresh fruits are less

consumed due to their astringent taste, but these are used in food industry in large scale for production of juices, nectars, jams, jellies, wines, and other dietary supplements (Sidor and Gramza-Michalowska 2019). A comparative study on the total phenolic (TP) content and the total flavonoid (TF) content in the fruit juices from the fruits of black chokeberry collected in three harvest seasons, August 2012, August 2013, and August 2014 from an orchard in Donja Zelina, Croatia, revealed that both TP and TF were found high in the growing season 2012 (11093 mg GAE/l and 9710 mg GAE/l, respectively) and lowest in the season 2014 (8834 mg GAE/l and 6994 mg GAE/l, respectively). Possibly bright sunshine and dry climate with less seasonal rainfall during the growing season 2012 have a positive impact on the high concentrations of phenolic compounds including flavonoids in the fruits (Tolic et al. 2017). Sunlight has been found to regulate the gene expression related to increased synthesis of anthocyanins and flavonoids in plants. Solar UV radiation increases plasma membrane NADPH oxidase activity via ROS production in apple peel to increase anthocyanin synthesis by increasing the activity of dihydroflavonol 4-reductase (DFR) and UDP-glucose: flavonoid 3-*O*-glucosyltransferase (UFGT) (Zhang et al. 2014a). Another study on the role of light-induced expression of myeloblastosis-related protein B (MYB) genes in anthocyanin and flavonoid synthesis in wild red-fleshed apples (*Malus sieversii* f. *niedzwetzkyana*) reveals that two putative genes MYB12 and MYB 22 are expressed in high concentrations and their overexpression promotes the accumulation of proanthocyanidins and flavonols in apple callus through upregulating the activity of the genes, leucoanthocyanidin reductase (LAR), and flavonol synthase (FLS), respectively (Wang et al. 2017b). In diffused sunlight having low UV-B light, the ripening of apples is delayed, fruit size decreased, and both anthocyanins and flavonoids content are reduced (Henry-Kirk et al. 2018; Chen et al. 2019a). Similarly, exposure of grape berry (*Vitis vinifera* L) clusters to low-temperature sunlight in post-veraison (onset of ripening) stage increases anthocyanin accumulation in grape skin by upregulation of the expression of MYB 12 gene and its target genes related to anthocyanins and flavonols biosynthesis, whereas high-temperature sunlight increases the degradation of anthocyanins in grape skin as well as decreases the expression of flavonoid synthesis related genes. Thus, exposure of grape clusters to sunlight during the morning hours up to midday at the ripening stage is recommended to increase both anthocyanins and flavonols contents in ripe grapes. Sunlight exposure significantly increases the levels of delphinidin-, cyanidin-, petunidin-, peonidin-, and malvidin-3-*O*-glucosides (**30**–**34**) throughout the stages of berry ripening (Matus et al. 2009).

The maritime climate (mild summer) has a significant role to enhance the concentrations of phytochemicals in fruits and vegetables that are grown in summer in Southern Hemisphere, compared to those grown in Northern Hemisphere. The high levels of anthocyanins in cherries, nectarines, peaches, and plums as well as high levels of carotenoids in red bell peppers and nectarines and high levels of ascorbic acid in cherries, peaches, red bell peppers, and carrots are found in these crops that are grown in summer season in Otago, New Zealand, compared to those grown in summer in the US, Northern Greece, Spain, and Finland (Leong and Oey 2012).

The young and tender leaves of tea (*Camellia sinensis* L) are consumed as beverage to reduce the risk of various diseases including cardiovascular diseases, cancers, obesity, diabetes, and Alzheimer disease. The major constituents of green tea, such as phenolic compounds, including catechins (mainly epigallocatechin gallate (EGCG **35**), epigallocatechin (EGC **36**), epicatechin gallate (ECG **37**), gallocatechin (GC **38**), epicatechin (EC **39**), and catechin (C **40**)), flavonol glycosides, anthocyanidins, phenolic acids and caffeine, and their antioxidant property in tea are influenced by a variety of environmental factors, such as geographical location of cultivation, atmospheric temperature, rainfall, amount of sunlight, fertilization, soil type, and plucking standard and frequency. Green tea contains unoxidized polyphenols, whereas black tea contains both native unoxidized polyphenols and oxidized theaflavins (TFs) and thearubigins (TRs). The concentrations of flavonoids in fresh apical shoots of tea cultivated in cold season in Central Africa are high, whereas in Japan, the concentrations of EC and EGC are high in teas grown in spring season, and the concentrations of ECG and EGCG are high in teas grown in summer season. In China, the concentrations of EGC, C, GC, and EC are high in teas grown in spring season than those grown in autumn season. Tea cultivation in extreme rainfall in monsoon (summer) season compared to spring drought season reduces the functional quality of tea up to 50% by reducing the concentrations levels of catechins and methylxanthines (caffeine **41**, theobromine **42**, and theophylline **43**). Rapid growth of tea leaves in monsoon season decreases the concentrations of tea phenolic compounds including catechins and methylxanthines through a dilution effect. Hence, tea consumers prefer spring tea to get better flavor and functional quality (astringency, bitterness, and sweetness) of teas. Shade treatment of tea leaves during cultivation of tea plants improves the quality of tea beverage by reducing the levels of some flavonoids, particularly proanthocyanins and *O*-glycosylated flavonols by 53.4% and 43.3%, respectively, and astringency and increasing the concentrations of phenolic acids compared to sunlight exposed tea leaves (Ahmed et al. 2014; Wang et al. 2012a; Ku et al. 2010; Chen et al. 2010; Nakagawa and Torii 1964). Tea cultivation in high altitudes also influences the concentrations of phytochemicals in tea. Tea grown in high altitude has low levels of total polyphenols, particularly low levels of EGCG and ECG, and high levels of amino acids especially theanine, glutamic acid, arginine, serine, γ-aminobutyric acid, and aspartic acid, and thereby the tea possesses good flavor and taste (Han et al. 2017).

Both genotype and environmental effects have been shown to influence the composition and levels of phytochemicals in commercially cultivated coffee cultivars, *Coffea arabica* and *C. canephora*, mainly grown in Africa, Brazil, and India. The beverage quality of coffee depends on geographical origin and growth conditions, mainly shading and altitude in cultivation stage. Robusta coffee (*C. canephora*), mainly grown in India and Africa, has a higher caffeine content compared to Arabica (*C. arabica*), mainly grown in Brazil. The shade grown coffee improves the size of coffee beans and uniform ripening of berries and flavor by increasing the levels of caffeine and chlorogenic acids. High-altitude slope with morning sunlight in coffee cultivation increases the beverage quality of coffee by

increasing the levels of caffeine, trigonelline, and chlorogenic acids (Avelino et al. 2005; Vaast et al. 2006; Cheng et al. 2016).

4.3.4 Harvesting Effect

The total phenolic (TP) compounds and total anthocyanins (TA) contents of berry fruits at the time of harvest depend on the maturity stages. For example, the TP content of raspberries (*Rubus idaeus*) is decreased by 45% from green (unripe) to pink (semi-ripe) stage, while its TA content is increased by 129% from pink to ripe stage due to high anthocyanins content, whereas in blackberries (*Rubus fruticosus*) and strawberries (*Fragaria* × *ananassa*) fruits, the total phenolic content is decreased by 23% and 65%, respectively, from green to ripe stage (Wang and Lin 2000). In high bush blueberries (*Vaccinium corymbosum*), the TP content is decreased and TA content is increased by about 34% from green to ripe stage. Among the phenolic compounds, the contents of flavonols and hydroxycinnamic acids are decreased significantly from green to ripe stage due to their conversion into anthocyanins (Rodarte Castrejon et al. 2008). Hence, harvesting at the ripe stage of the berry fruits gives high levels of anthocyanins in fruits.

Harvested young tea twigs by plucking of one bud and three leaves (tri-leaves) and one bud and four leaves (quad-leaves) are better material for production of green tea or for production of fermented juice for black tea than the plucking of one bud and one leaf (mono-leaf) and one bud and two leaves (di-leaves) process. The former plucking process increases the levels of catechins and amino acids in green tea and the levels of theaflavins and thearubigins, amino acids, and soluble solids in black tea and thereby improves the sensory quality of tea. In black tea, theaflavins are mainly responsible for the astringency, brightness, color, and briskness of tea (Tang et al. 2018).

4.3.5 Postharvest Storage Effect

Postharvest storage of fruits and vegetables influences the concentrations of phytochemicals present in fruits and vegetables because of the decomposition of phytochemicals on storage condition and temperature induced lipid peroxidation and nonenzymatic browning processes in open atmosphere.

The storage of potato tubers (*Solanum tuberosum*) at low temperatures (near 4°C) increases sweetness of potatoes by breakdown of reserve starch into reducing sugars glucose and fructose. These high reducing sugar contents in potatoes negatively affect on the quality of processed products, such as chips and French fries. This cold-induced sweetening is also observed in ripe tomato (*Solanum lycopersicum*) storage because of similar genomes (Schreiber et al. 2014). However, the storage of potato tubers at 4°C prevents from the loss of its carotenoids and phenolics contents and antioxidant property (Blessington et al. 2010). Broccoli florets after packing in micro-perforated polypropylene bags and stored under open ambient condition at

15°C for a period of 144 h showed lower losses of chlorophyll, vitamin C, β-carotene, and total antioxidant contents than those stored under refrigerated condition (4°C) (Nath et al. 2011). Harvested broccoli on storage under controlled atmosphere (CA) or modified atmosphere packaging (MAP) prevents the loss of glucosinolate content (Jones et al. 2006). Small berries such as strawberries, red currants, and raspberries and cherries on storing at both room temperature (25°C) and refrigerating temperature (4°C) preserved the marketable qualities of fruits. Different cultivars of plums on storing in cold at 2°C for 35 d followed by shelf-life storage for 4 d at 20°C protected the fruits from the loss of phenolics, anthocyanins, and carotenoids contents as compared with freshly harvested fruits (Diaz-Mula et al. 2009).

4.3.6 Packaging Effect

Several studies demonstrate that CA or MAP packaging with low oxygen and high CO_2 concentrations or coating with edible chitosan on harvested fruits and vegetables is effective to maintain their freshness and prevents the loss of phytochemicals content by reducing the respiration rate of the enzymes. For instance, harvested carrots in both coating with chitosan and CA or MAP maintain the levels of carotenoids and phenolics in shelf-life storage (Simoes et al. 2009). Hot water treatment (46°C for 75 min) of harvested mangoes plus CA packaging prevents the loss of polyphenolic, such as gallic acid (**44**) and tannins content in mangoes (Kim et al. 2007). Harvested mushrooms on MAP with high oxygen concentrations (about 80%) improves shelf-life storage with freshness and antioxidant property up to 30 days (Wang et al. 2011a).

4.3.7 Chemical Treatment Effect

Plant growth hormone, 1-methylcyclopropene (1-MCP), is widely used in postharvest storage technologies to maintain freshness and prevent ripening of fruits and vegetables. It acts as ethylene antagonist and binds with the receptors of ethylene present in fruit tissues and blocks the ethylene-mediated processes of ripening, softening, and early senescence of fruits. Its efficiency depends on several factors, such as concentration, exposure duration, and maturity stage of harvested cultivars. Moreover, it enhances the antioxidant potential in fruits due to its ROS scavenging activity (Lata et al. 2017). Both 1-MCP treatment and CA storage condition of harvested matured mangoes maintain total phenolic and flavonoid contents and freshness and improve shelf-life storage of mangoes (Sivakumar et al. 2012). A similar combined 1-MCP treatment and CA storage condition at 0°C on 'Cripps Pink' apples maintain both phenolic content and total antioxidant property during long-term storage up to 160 days (Hoang et al. 2011). In case of sweet cherries (*Prunus avium* L), a treatment of both 1-MCP and hexanal enhances the quality and shelf-life of the cherries without significant loss of polyphenolics content. Hexanal, a

natural volatile aldehyde, inhibits the activity of phospholipase D enzyme in membrane degradation of fruit tissues during ripening and senescence processes (Sharma et al. 2010).

4.3.8 Processing Effect

Fruits and vegetables are processed to meet consumer's requirement and to increase their shelf-live for use in off-seasons. Major industrial processing of fruits and vegetables include blanching (heating), canning, sterilizing, and freezing as well as some cooking methods, such as boiling, steaming, and microwaving. Such processing normally reduces the content and alters the composition of nutrients including phytochemicals in processed foods. In conventional domestic cooking of red cabbage, only 32.7–64.5% of available 45.7–66.9% of total phenolics are retained in cooked food (Podsedek et al. 2008). The effects of food processing, such as blanching (98°C, 10 min), freezing (−20°C) and freeze-drying on the contents of anthocyanins, carotenoids, and vitamin C in some summer fruits (cherries, nectarines, apricots, peaches, plums) and vegetables (carrots and red bell peppers), have been reported. Blanching and freezing enhanced the contents of anthocyanins after processing compared to fresh commodities. Possibly, during processing stage, the plant cell membrane-bound anthocyanins are released to enhance their bioavailability. Moreover, the concentration of vitamin C was increased on heating process due to inactivation of ascorbic acid oxidase. Blanching also increased the anthocyanins content in cherries, peaches, and plums (Leong and Oey 2012). Blanching (95°C, 2 min) prior to pursee/juice processing of blueberries improves the phenolics and anthocyanins contents (Sablani et al. 2010). Only freezing of broccoli and carrots at 4°C for 7 days increased the total phenolics content but decreased ascorbic acid content, whereas both of their blanching (95°C, 3 min) and freezing retained both phenolic and ascorbic acid contents (Patras et al. 2011).

Fruiting bodies of several edible mushrooms are subjected to drying process in hot air or microovens at different temperatures for their storage for a longer time and to use all the year round. This drying process significantly affects the contents of phenolics, organic acids, polysaccharides, vitamins, and micronutrients, compared to fresh samples. Drying at air temperature for 7 days significantly increases the total phenolic (TP) content (8.77–119.8 mg GAE/g of dw) in the mushroom, *Amanita zambiana*, due to release of cell wall bound polyphenols as a result of cell wall destruction on drying (Reid et al. 2017). However, microoven drying at 43°C did not affect on TP or total flavonoid (TF) content in mushroom, *Pleurotus ostreatus* (Mutukwa et al. 2019). Microoven drying at higher temperature, 70°C, results 17% reduction in TP (3.79 to 3.14 mg GAE/g of dw) in *Hericium erinaceus*, and 40% reduction of TP (1.89 to 1.14 mg GAE/g of dw) in *Leccinum scabrum*, compared to fresh samples (Gasecka et al. 2020). Therefore, microoven drying at lower temperatures prevents the loss of phenolic contents in dried mushrooms.

The processing steps of both green and black teas play an important role to maintain their sensory quality and the content and composition of antioxidant phytochemicals, such as catechins in green tea and theaflavins, thearubigins, and flavonol glycosides in black tea.. The high content of catechins, EGCG, and ECG in green tea and high contents of theaflavins (TFs), particularly theaflavin 3,3′-di-*O*-gallate (TF-3,3′G **45**) and theaflavin 3-*O*-gallate (TF-3G **46**) in black tea, are the indicators of the quality of green and black teas. In green tea, the levels of EGCG and ECG are increased by about 2-fold in roasting process compared to that in fresh tea leaves. Possibly, high-temperature roasting process increases the epimerization of catechins to epicatechins, which on abstraction of gallate moiety from gallic acid/theogallin increases the yield of EGCG in roasted tea leaves. In the production of green tea, roasting (250–300°C, 10 min), rolling (10 min), and three consequent drying (150–200°C, 100–150°C, 90–100°C, 10 min each) steps provide high contents of EGCG (**35**) and ECG (**37**) in green tea, whereas in black tea, both fermentation and drying steps play positive roles for high contents of TFs through conversion of catechins into TFs by oxidation (catalyzed by polyphenol oxidase, PPO) and condensation processes. In black tea, there was no significant change in the content of kaempferol and quercetin glycosides between the fresh leaf and the final product in fermentation process, whereas the triglycosides of myricetin were completely decomposed and monoglycosides of myricetin were reduced to half (about 38%) during the fermentation process. Similarly, the content of methylxanthines, caffeine, and theobromine was decreased significantly in the fermentation step. However, the total TFs content was increased in both fermentation and drying steps in black tea compared to fresh leaf (Lee et al. 2019b). A study on fermentation process in the production of black tea reveals that fermentation conditions at 35°C and pH 5.1 for 75 min duration using tri-leaves and quad-leaves of tea twigs provide maximum concentrations of TFs in the fermented juices (Tang et al. 2018). Another study reports that in black tea production, withering (room temperature (rt) drying, 24 h), rolling (30 min), fermentation (rt, 3 h), and two consequent drying (110°C, 20 min; 90–100°C, 10 min) steps provide high contents of TFs in black tea (Lee et al. 2019b).

4.4 Inherent Properties of Natural Products in Prevention and Treatment of Human Diseases

Overexpression of oxidants, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) in human body from excessive oxidative stress under various environmental factors, is responsible for the pathogenesis of many chronic diseases including obesity, diabetes, cancers, cardiovascular diseases, and neurodegenerative diseases. The scavenging of these oxidants is thought to be an effective measure to reduce the level of oxidative stress and to exert a protective effect against the development of these chronic diseases. A growing piece of literature demonstrates that fruits, vegetables, and whole grains on dietary intake exert a protective effect against the development of these chronic diseases. Various classes of antioxidant

phytochemicals present in plant food (fruits, vegetables, and grains) and other medicinal plants, animals, and microorganisms are considered to be responsible to possess preventive roles against these chronic diseases and have health benefit effects. These phytochemicals reduce the oxidative stress through scavenging the free radicals and inducing anti-inflammatory action. These antioxidant phytochemicals are produced by the plants, animals, and microorganisms for their protection and survival under odd extreme environmental stress conditions in their habitats. The major identified antioxidant phytochemicals include polyphenolic compounds (e.g., flavonoids, phenolic acids, stilbenes, tannins, and coumarins), terpenoids, carotenoids, steroids, saponins, glucosinolates, and alkaloids. The flavonoids are subclassified into flavonols, flavones, flavanols, flavanones, anthocyanidins/anthocyanins, and isoflavonoids. The terpenoids are subclassified into monoterpenoids, sesquiterpenoids, diterpenoids, and triterpenoids (Zhang et al. 2015; Harborne and Mabry 1982; Finar 1995).

Metabolic inflammation, a low-grade chronic pro-inflammatory environment in metabolic tissues during nutrient excess, has emerged as an important event in the development of obesity, type 2 diabetes, and cardiovascular diseases (CVDs). Macrophages, endoplasmic reticulum stress, and NLRP3 inflammasome are the major inflammatory effectors that contribute to insulin resistance and atherosclerosis and are considered as precursors of obesity, type 2 diabetes, and CVDs. These antioxidant phytochemicals reduce metabolic inflammation in metabolic tissues by increasing insulin action and insulin secretion in pancreatic beta cells through AMPK activation and other signaling pathways. Moreover, these phytochemicals modulate gut microbiota composition to reduce metabolic inflammation, improve insulin secretion and insulin sensitivity in metabolic tissues, and improve immunity of the intestine for protection from the entry of toxic pathogens from the gut (Steinberg and Schertzer 2014).

Several phytochemicals isolated from plant food, herbs, animals, and microorganisms have been shown to possess antiobesity and antidiabetic effects equal to and even more potent than known antiobese drugs and oral hypoglycemic agents. These bioactive phytochemicals from nature might offer a key to unlock the nature's strategy in the synthesis of natural molecules of chemical structural diversity and new therapeutic targets in prevention of the development of obesity, diabetes, and their associated complications in humans (Karri et al. 2019; Fu et al. 2016; Qi et al. 2010; Jung et al. 2006).

4.5 Major Therapeutic Targets of Natural Products in Obesity Treatment

4.5.1 Lipase Inhibitory Effect

A growing body of evidence demonstrates that obesity can be prevented by reducing energy intake or by increasing energy expenditure through maintenance of energy homeostasis in the body. The energy intake can be reduced by either reducing

nutrient digestion and absorption of digested nutrients or reducing food intake. Dietary fat, one of the major sources of calorie intake, is absorbed in the intestine by the action of pancreatic lipase. Pancreatic lipase is a key enzyme for absorption of dietary triacylglycerols via hydrolysis to monoacylglycerols and fatty acids. A wide variety of plants and microorganisms extracts and their active phytochemicals have been reported to exhibit pancreatic lipase inhibitory effect. These phytochemicals and herbal/microbial extracts resemble the function of orlistat (**46a**), currently used lipase inhibitor for obesity treatment, but their inhibitory mechanisms are different from that of orlistat; some act as inhibitors in a reversible manner, while others as irreversible manner, similar to orlistat (Birari and Bhutani 2007).

4.5.2 Suppressive Effect on Appetite

A wealth of information indicates that the food intake in humans and rodents is regulated by a complicated central and peripheral neuroendocrine signaling pathways involving approximately 40 orexigenic (appetite stimulating) and anorexigenic (appetite suppressing) hormones, neuropeptides, enzymes, and other chemical signaling molecules and their receptors. Neuropeptide Y (NPY), agouti-related peptide (AgRP), and melanin-concentrating hormone (MCH) are orexigenic signaling molecules and are upregulated on fasting, whereas pro-opiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART), serotonin (5-HT), histamine, dopamine (DA), and noradrenaline (NE) are anorexigenic molecules, and their upregulation in brain increases satiety in the hypothalamus. Excessive nutrient intake-induced insulin resistance in obese brain, FoxO1 gene transcriptionally increases orexigenic neuropeptide AgRP via G-protein-coupled receptor 17 (GPR17) and decreases anorexigenic neuropeptide POMC via carboxypeptidase E (CPE) for increased food intake (Ren et al. 2012; Plum et al. 2009; Atkinson 2008). The gastrointestinal (GI) tract, the largest endocrine organ in humans, releases more than 20 peptide hormones to regulate appetite by inducing signals for a sense of starvation before a meal and satiety after a meal in healthy nonobese humans (Murphy and Bloom 2006). Ghrelin, an appetite-stimulating hormone, is secreted from the stomach on fasting, whereas GI tract secretes some anorexigenic peptide hormones including peptide YY (PYY), CCK, and GLP-1 to suppress appetite and to reduce food intake. Cholecystokinin (CCK) stimulates gallbladder contraction and pancreatic and gastric secretions to reduce energy intake. Glucagon-like peptide-1 (GLP-1) stimulates insulin release and reduces food intake (Yang et al. 2008; Naslund and Hellstrom 2007; Drucker 2006). Many phytochemicals and plant extracts reduce the food intake in animal models by reducing the expression of ghrelin or NPY or AgRP and increasing the expression of GLP-1 or CCK-8 in intestine or POMC in hypothalamus (Table 4.1).

Table 4.1 List of some natural products (extracts/active components isolated from various natural sources) having reported anti-obesity effects and their major molecular targets and actions

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
A. Plant source				
1. Actinidaceae				
Actinidia arguta	Roots (EtOAc), ursolic acid **52** (Fig. 4.1)	Cellular, rat fat cells	Anti-lipase activity, lipolysis↑, AT mass↓	Kim et al. (2009)
Actinidia polygama	Fruits (70% EtOH)	HFD-fed obese mice	Serum TG, leptin↓	Sung et al. (2013a)
2. Apiaceae				
Ferula asafoetida	Gum (aqueous)	Obese diabetic rats	AT (abdominal) fat and adipocytes size↓, Serum leptin↓, Lipid metabolism↑	Azizian et al. (2012)
Angelica keiskei	Leaves, stems (90% EtOH)	Obese diabetic rats	Serum, liver G↓, liver ACOX, MCAD↑	Ohnogi et al. (2012)
Peucedanum japonicum	Leaves EtOH, 50% EtOH), neochlorogenic acid (**53**), chlorogenic acid (**21**), rutin (**54**), pteryxin (**55**)	Obese diabetic mice 3T3-L1 cells	Lipase activity↓, energy expenditure↑, lipid metabolism↑, UCP3, PPARα, CPT1α, GLUT4↑, Adipogenesis↓	Nukitrangsan et al. (2012), Nugara et al. (2016), Taira et al. (2017)
3. Amaranthaceae				
Amaranthus dubius	Leaves (MeOH)	Obese mice	AT mass, serum TG↓	Nderitu et al. (2017)
4. Apocynaceae				
Alstonia boonei	Stem bark (EtOH)	Obese rats	Food intake, AT mass↓ Serum TC, LDL, leptin↓	Onyeneke and Anyanwu (2014)
Oroxylum indicum	Bark (ethyl acetate), oroxylin A (**56**), chrysin (**57**), baicalein (**58**)	3T3-L1 cells, lipase inhibition assay	Adipogenesis, expression of PPARγ, C/EBPα, SREBP-1c in 3T3-L1 cells↓, Pancreatic lipase activity↓	Mangal et al. (2017)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
Tabernaemontana divaricata	Aerial parts (MeOH)	HFD-fed obese rats	Serum lipids, liver, body mass↓	Kanthlal et al. (2012)
5. Amaryllidaceae				
Allium sativum	Stem (EtOH)	HFD-fed obese mice	Lipid metabolism, antioxidant status↑ Plasma lipid, leptin↓, liver TG, lipogenic genes↓ Lipid metabolism↑	Kim et al. (2013)
	Bulb oil	Obese mice	Hepatic lipid mass↓, PPARα↑	Lai et al. (2014)
6. Alismataceae				
Alisma orientale	Rhizomes (EtOH), triterpenoids	OP9 preadipocytes	Adipogenesis↓, PPARγ, C/EBPα, FAS, aP2, HSL↓	Park et al. (2014)
		Hyperlipidemic mice	Lipid metabolism↑ Serum lipids, lyso-PC↓	Li et al. (2016)
7. Araliaceae				
Acanthopanax senticosus	Fruits (EtOH), copteroside B (**59**), gypsogenin-3-O-Glc A (**60**), silphioside F (**61**)	HFD-fed obese mice	Lipid metabolism↑ Liver AMPK, PPARα↑ Hepatic lipid mass, lipogenesis↓	Saito et al. (2016)
		Enzyme assay	Pancreatic lipase activity↓	Li et al. (2007)
A. sessiliflorus	Leaves (EtOH) Sessiloside (**62**) Chiisanoside (**63**)	Enzyme assay	Pancreatic lipase activity↓	Yoshizumi et al. (2006)
Aralia elata	Shoots (70% EtOH), saponins	HepG2 cells, HFD-fed obese mice	Intracellular lipid mass↓, lipid metabolism↑, PPARα, CPT1, ACC2↑, SREBP1, FAS, ACC1↓, serum glucose, TG, hepatic fat↓	Huang et al. (2015)

Panax ginseng	Berry (75% EtOH), ginsenosides, ginsenoside Re (**64**)	Obese diabetic mice	Food intake, body weight, serum glucose, TC↓, energy expenditure↑ Adipogenesis↓	Attele et al. (2002)
	Dry leaves (aqueous), saponins	3T3-L1 cells, HFD-fed obese Rats	Food intake, AT mass, lipogenesis↓,PPARγ, C/EBPα, LPL, aP2↓	Lee et al. (2017b)
P. quinquefolius	Leaves, stems (aqueous) Saponins, ginsenoside Rb1 **65**	HFD-fed obese mice, enzyme assay	Food intake, body fat↓ Energy expenditure↑, central leptin signaling↑ Hopothalamic SOCS3, PTP1B↓, NPY, AgRP↓, PYY, POMC↑, pancreatic lipase activity↓	Liu et al. (2008), Liu et al. (2010b), Xiong et al. (2010), Wu et al. (2014b)
8. Asparagaceae				
Agave angustifolia, *A. potatorum*	Leaves (80% ethanol and water), agavins (oligofructosides)	Obese mice	Lipid metabolism↑ Food intake↓ Body fat mass, serum TG, TC, LDL-C, gastric ghrelin secretion↓ Serum HDL-C, GLP-1, colon SCFAs↑	Santiago-Garcia and Lopez (2014)
Liriope spicata var. *prolifera*	Tuberous roots (aqueous), polysaccharides fr	Obese diabetic mice	Lipid metabolism↑ Serum TC, TG, LDL, hepatic TG↓	Liu et al. (2013b)
Polygonatum falcatum	Rhizomes (EtOH), kaempferol **66**	3T3-L1 cells	Adipogenesis↓, PPARγ, SREBP1c, LXRβ↓	Park et al. (2012)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
9. Asteraceae				
Eclipta alba	Whole plant (EtOAc fr), ecliptal (**67**)	3T3-L1 cells HFD-fed obese hamsters	Adipogenesis↓, Cell cycle proteins CDK2/4/6, cyclin D1/D3↓ Adipogenic genes PPARγ, C/EBPα, FAS, FABP4↓, serum lipids, hepatic lipid mass↓	Gupta et al. (2017, 2018)
Artemisia princeps	Aerial parts (EtOH), chlorogenic acid (**21**)	HFD-fed obese diabetic mice	Lipid synthesis↓, plasma lipids, leptin, hepatic lipid mass↓, hepatic FAS↓	Yamamoto et al. (2011)
A. vulgaris	Whole plant (70% MeOH)	Hypercholesterolemic rats	Lipid synthesis↓ Serum lipids, hepatic lipid mass↓, hepatic HMGCR↓	El-Tantawy (2015)
Taraxacum officinale	Leaves (60% EtOH)	3T3-L1 preadipocytes, enzyme inhibition assay	Adipogenesis↓, pancreatic lipase activity↓, serum lipids, hepatic lipid mass↓ Liver, muscle p-AMPK↑, lipid metabolism↑	Zhang et al. (2008), Davaatseren et al. (2013), Marta et al. (2014)
10. Asphodelaceae				
Aloe vera	Leaves (gel powder), phenolic acids	HFD-fed obese mice	Energy expenditure↑, WAT mass, serum glucose, TG, TC↓, adiponectin, AMPK↑	Pothuraju et al. (2016)
11. Basellaceae				
Boussingaultia gracilis var. *pseudobaselloides*	Leaves (EtOH)	HFD-fed obese rats, 3T3-L1 cells	Lipid metabolism, energy expenditure↑ Hepatic lipid mass, fat pad mass, serum lipids↓ Hepatic PPARγ, FAS, SREBP-1c↓, PPARα, CPT1, UCP2↑ Adipogenesis↓, p-AMPK↑	Wang et al. (2011b), Kim and Choung (2012)

12. Betulaceae				
Betula platyphylla var. *japonicum*	Bark (80% methanol, butanol fr) Phenylglycosides, platyphylloside (**68**), arylbutanoid glycosides (A-C **69–71**)	3T3-L1 cells	Adipogenesis, intracellular lipid content, expression of PPARγ, C/EBPα, SREBP-1c, SCD1, FAS, aP2, perilipin, LPL↓ Expression of lipolysis and insulin signaling-related genes HSL, ATGL, adiponectin, GLUT4↑	Lee and Sung (2016), Huh et al. (2018)
13. Bignoniaceae				
Tecomella undulata	Bark (EtOAc), ferulic acid (**72**), rutin (**54**)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis↓, intracellular TG mass, PPARγ, C/EBPα, E2F1, leptin, LPL↓, body weight, plasma lipids↓, hepatic SIRT1, plasma adiponectin↑, lipid metabolism↑	Alvala et al. (2013), Kumar et al. (2012)
14. Bombacaceae				
Bombax ceiba	Stem-bark (MeOH), lupeol (**73**), flavonoids	HFD-fed obese rats	Thermogenesis, lipid metabolism↑, body fat mass, serum lipids, hepatic lipid mass, TBARS↓, hepatic FAS, PTP1B↓, AMPK↑	Gupta et al. (2013)
15. Brassicaceae				
Brassica juncea	Leaves (80% EtOH)	HF, HC-diet fed obese rats	Lipid metabolism, lipid excretion↑, liver, AT mass, serum lipids↓, hepatic PPARα, LDLR, CYP7α1, fecal lipid excretion↑, hepatic FAS, ACC, GPDH↓	Lee et al. (2018b)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
Wasabia japonica	Leaves (water)	3T3-L1 cells, HFD-fed obese diabetic mice	Adipogenesis↓'Intracellular TG mass, PPARγ, C/EBPα, GPDH, aP2↓ Lipid metabolism↑, WAT, liver fat mass, serum TG, TC, leptin↓ Serum adiponectin, liver ACOX1, PPARα↑, liver PPARγ, SREBP1c, ACC, FAS, HMGCR↓	Ogawa et al. (2010), Yamasaki et al. (2013)
16. Campanulaceae				
Adenophora triphylla var. *japonica*	Roots (EtOH)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis↓, intracellular TG, accumulation, PPARγ, FAS, aP2↓ Lipid metabolism↑ Oxidative stress↓ AT, liver fat mass, serum TG, LDL-C, glucose, insulin Liver TNFα, GPDH, PPARγ, SREBP-1c, LPL↓, adiponectin, AMPK, PPARα, CAT, SOD↑	Lee et al. (2013a, 2015)

Platycodon grandiflorus	Roots (EtOH), platycosides, platycodin D (**74**), deapioplatycodin D (**75**), platycodins A, C (**76**, **77**)	3T3-L1 cells, HepG2 cells, HFD-fed obese mice	Adipogenesis, pancreatic lipase activity, hepatogenesis↓, lipid metabolism, thermogenesis↑, body fat mass, plasma lipids, leptin, hepatic TG↓, thermogenesis-related genes AMPK, SIRT1, PPARα, PGC-1α, UCP1↑, lipogenesis genes FAS, SCD1, ME, PAP, G6PD↓, gluconeogenic genes PEPCK, G6Pase↓	Kim et al. (2016b), Hwang et al. (2013), Lee et al. (2012a), Xu et al. (2005)
17. Caprifoliaceae				
Lonicera caerulea var. *edulis*	Berries (powder), flavonoids, anthocyanins	HFD-fed obese mice	Lipid metabolism, hepatic antioxidant status↑, serum lipids, leptin, glucose, AST, ALP, LDH, body fat mass↓, hepatic AMPK, GSH, CAT, SOD↑, hepatic ACC, C/EBPα, SREBP-1c, G6Pase, PEPCK↓	Kim et al. (2018a)
18. Celastraceae				
Salacia oblonga	Roots (aqueous)	Zucker obese diabetic rats	Lipid metabolism↑, hepatic lipid mass, serum lipids, glucose↓, hepatic PPARα, CPT1, ACOX↑	Huang et al. (2006)
S. reticulata	Roots (hot water), catechins	Tsumura Suzuki obese diabetes (TSOD) mice, 3T3-L1 cells	Lipid synthesis↓, visceral and subcutaneous fat mass, serum lipids, liver TG content↓, serum adiponectin, liver HSL↑ Adipogenesis↓, PPARγ, C/EBPα, LPL, aP2, CD36, GPDH↓, p-AMPK, adiponectin, ATGL↑	Shimada et al. (2011, 2014), Akase et al. (2011)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
Tripterygium wilfordii	Root-bark, celastrol **78**, triptolide **79**	3T3-L1 cells, HFD-fed ob/ob mice	Adipogenesis↓, intracellular lipid mass, PPARγ2, C/EBPα, ATGL, p53↓ Energy expenditure, glucose and lipid metabolism↑, central leptin sensitivity↑, food intake, body fat mass, serum TG, TC, LDL-C, central SOCS3↓, BAT, muscle HSF1, PGC-1α, UPC1, CPT1α, PRDM16↑	Wang et al. (2020b), Choi et al. (2016), Ma et al. (2015b), Liu et al. (2015a), Liu et al. (2011)
Euonymus alatus	Roots (50% EtOH)	HFD-fed obese mice	Food intake, lipogenesis↓, hepatic fat mass, lipogenic genes PPARγ, SREBP-1c, FAS, GAPT↓	Park et al. (2005)
19. Combretaceae				
Terminalia bellirica	Fruits (hot water), gallic acid	TSOD mice, lipase enzyme inhibition assay	Lipid metabolism↑, pancreatic lipase activity↓, plasma and hepatic TG content↓	Makihara et al. (2012)
T. paniculata	Bark (EtOH), triterpenoids, ellagic acids	HFD-fed obese rats	Lipid metabolism↑, AT and liver fat mass, serum lipids, leptin, AST, ALT, ALP, hepatic FAS, PPARγ, SREBP-1c↓, serum adiponectin, liver AMPK-1α↑	Mopuri et al. (2015)
T. sericea	Roots, leaves (aqueous), sericoside (**80**)	3T3-L1 cells, fructose-fed obese rats	Adipogenesis↓, lipolysis↑, visceral fat, serum and liver TG content↓	Lembede et al. (2019), Mochizuki and Hasegawa (2006)

20. Cannabaceae				
Humulus lupulus	Pomace (water), humulone (**81**), xanthohumol (**82**)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis↓, lipid metabolism↑ AT mass, adipocyte size, plasma TC, liver TG, TC, PPARγ, SREBP-1c↓, PPARα↑	Takahashi and Osuda (2017), Sumiyoshi and Kimura (2013)
21. Clusiaceae				
Garcinia cambogia	Fruits (commercial ext.), (-)-hydroxycitric acid **83**	3T3-L1 cells, HFD-fed obese mice	Adipogenesis↓, food intake↓, lipid metabolism↑, visceral fat mass, serum TG, TC, glucose, leptin, TNFα, AT SREBP-1c, C/EBPα, aP2, PPARγ2, ATP citrate lyase↓, central serotonin↑	Chuah et al. (2013), Kim et al. (2008a), Sullivan et al. (1977)
22. Cornaceae				
Cornus mas	Fruits (methanol), ursolic acid (**52**), anthocyanins	HFD-fed obese mice	Lipid metabolism↑, serum glucose, TG, hepatic TG content↓, islet mass and function↑	Jayaprakasam et al. (2006)
23. Cucurbitaceae				
Coccinia grandis	Roots (ethanol, hexane fr)	3T3-L1 cells	Adipogenesis↓, intracellular lipid mass, PPARγ, C/EBPα, FAS, LPL, aP2, GLUT4↓	Bunkrongcheap et al. (2014)
Momordica charantia	Green fruits (fermented juice, both aq. and ethanol ext.), polysaccharides, saponins, triterpenes	HFD-fed obese rats and mice	Lipid metabolism and antioxidant status↑ AT fat mass, serum TG, TC, LDL-C, leptin, FFAs↓, serum HDL-C, adiponectin↑	Wen et al. (2019), Wang and Ryu (2015)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
24. Cupressaceae				
Juniperus chinensis	Heartwood (hot water)	HFD-fed obese rats	Thermogenesis and lipid metabolism↑, visceral fat mass, plasma lipids (TG, TC, LDL-C, VLDL, FFAs), leptin, insulin↓, plasma HDL-C, AT p-AMPK, p-ACC2, UCP2, UCP3↑, AT ACC, PPARγ, SREBP-1c, FAS↓	Kim et al. (2008b)
25. Cynomoriaceae				
Cynomorium songaricum	Stem (ethanol), triterpenoids	HFD-fed obese mice	Thermogenesis and lipid metabolism↑, fat pad mass, serum glucose↓, muscle fatty acids oxidation, p-AMPK, PGC-1α, UCP2, UCP3, GLUT4↑	Chen et al. (2020)
26. Cyperaceae				
Cyperus rotundus	Rhizomes (hexane), sesquiterpenes	Zucker obese rats, 3T3-F442 cells	Thermogenesis and β3AR activity↑, adipogenesis↓	Lemaure et al. (2007)
27. Dioscoreaceae				
Dioscorea batatas	Tubers (50% ethanol)	HFD-fed obese mice	Lipogenesis and inflammation↓, viceral fat mass, serum and hepatic TG content, serum leptin, IL-6, TNFα, MCP-1, AT C/EBPα, CD36↓	Gil et al. (2015)

D. nipponica	Rhizomes (powder), saponins and sapogenins, dioscin (**84**), gracillin **85**, trillin (**86**), diosgenin **87**, prosapogenins A and C of dioscin (**88**, **89**)	HFD-fed obese rats, lipase enzyme inhibition assay	Lipid metabolism, antioxidant activity and fecal lipid excretion↑, pancreatic lipase activity and adipogenesis↓, fat mass of body, serum TG, VLDL-C, AT p-ERK1/2, SREBP-1c, C/EBPα, FAS, aP2↓, AT p-AMPK, p-ACC↑	Poudel et al. (2014), Wang et al. (2012a), Kwon et al. (2003)
D. oppositifolia	Tubers (ethanol ext., butanol fr or powder), polyphenolics, 3,5-dimethoxy-2,7-phenanthrenediol **90**, (3*R*,5*R*)-3,5-dihydroxy-1,7-*bis*(4-hydroxyphenyl)-3,5-heptanediol **91**	Lipase inhibition assay, HFD-fed obese mice	Pancreatic lipase activity, food intake↓, body weight gain, serum TG, TC, LDL-C, hepatic lipid content↓	Jeong et al. (2016), Yang et al. (2014b)
28. Elaeagnaceae				
Hippophae rhamnoides (seaberry)	Leaves (ethanol ext. or powder)	HFD-fed obese mice	Lipid and antioxidant metabolisms↑, epididymal fat mass, serum leptin, serum and hepatic TG, TC, hepatic ACC, CYP2E1↓, hepatic PPARα, CPT-1, SOD, CAT, fecal lipid excretion↑	Pichiah et al. (2012), Lee et al. (2011b)
29. Ericaceae				
Rhododendron groenlandicum (Labrador tea)	Leaves (80% ethanol), catechins, quercetin glycosides	HFD-fed obese mice	Lipid metabolism↑, serum glucose, liver TG content, SREBP-1c, p-IKK↓, muscle p-Akt, GLUT4, liver p-AMPK, PPARα↑	Ouchfoun et al. (2016)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
30. Ebenaceae				
Diospyros lotus	Leaves (water), gallic acid (**44**), flavonoids, myricitrin (**92**)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid accumulation↓, lipid metabolism↑, antioxidant activity↑, visceral fat mass, serum TG, TC, LDL-C, leptin, glucose, liver lipid content, MDA, AST, ALT↓, liver SOD, CAT, GP_x↑	Kim et al. (2019)
31. Fabaceae				
Acacia meansii	Bark (hot water), catechins	HFD-fed obese diabetic KK-Ay mice	Lipid metabolism and energy expenditure↑, WAT and liver lipid mass, plasma glucose, SGOT, SGPT, AT TNF-α, hepatic lipogenesis, SREBP-1c, ACC, FAS, PPARγ, LPL↓ Muscle PPARα, CPT1, ACOX, UCP3, GLUT4, AT adiponectin↑	Ikarashi et al. (2011)
Cassia tora	Seeds (ethanol)	HFD-fed obese rats	Lipid metabolism↑, WAT fat mass, plasma TG, TC, FFAs, AT FAS, ACC, SREBP-1c↓, AT p-AMPK, CPT1↑	Tzeng et al. (2013)
Glycyrrhiza uralensis	Roots (methanol ext., dichloromethane fr), licochalcone A (**93**), liquiritigenin (**94**)	HFD-fed obese mice, Lipase inhibition assay	Energy expenditure↑, inguinal fat pad mass, serum glucose, TC↓, WAT PGC-1α, UCP1, PRDM-16↑ Inhibition of pancreatic lipase activity by licochalcone A (IC_{50}, 35 μg/ml)	Lee et al. (2018a), Won et al. (2007)

Pueraria lobata	Roots (water ext. or powder), puerarin (**8**), daidzein (**95**), genistein (**96**)	HFD-fed obese mice	Energy expenditure and lipid metabolism↑, Serum glucose, LDL, AT ceramide↓, AT adiponectin↑	Buhlmann et al. (2019), Prasain et al. (2012)
Tamarindus indica	Fruits (aqueous pulp)	HFD-fed obese rats	Lipid synthesis↓ Anti-oxidant activity↑, serum TG, TC, LDL, leptin, MDA, liver fat mass↓, serum HDL, SOD, GP_x↑	Azman et al. (2012)
Glycine max	Seed-coat (ethanol), cyanidin-3-glucoside (**31**), delphinidin-3-glucoside (**30**), catechins, proanthocyanidins	HFD-fed obese mice, 3T3-L1 cells	Lipid metabolism and energy expenditure↑ Food intake↓, AT fat mass, plasma glucose, TNF-α, IL-6, MCP-1, AT ACC, C/EBPα↓, AT p-AMPK, LPL, HSL, UCP-1, UCP-2↑ Adipogenesis, intracellular lipid accumulation, PPARγ, LXRα, SREBP-1c, C/EBPα↓, PGC-1α, SIRT1↑	Kim et al. (2012b, 2015), Kanamoto et al. (2011)
32. Gentianaceae				
Gentiana lutea	Roots (30% ethanol), loganic acid (**97**), gentiopicroside (**98**)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid mass, C/EBPα, adiponectin, GLUT4↓ AT and liver fat mass, serum leptin↓	Park et al. (2020a)
33. Geraniaceae				
Geranium thunbergii	Leaves (70% ethanol), flavonoids	HFD-fed obese mice	Lipid synthesis↓, AT mass, adipocyte size, serum TG, TC, LDL-C, leptin, AT SREBP-1c, PPARγ, FAS, aP2↓	Sung et al. (2011)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
34. Ginkgoaceae				
Ginkgo biloba	Leaves (commercial ext.), ginkgolide C (**99**), bilobetin (**100**), ginkgetin (**101**), isoginkgetin (**102**), sciadopitysin (**103**)	3T3-L1 cells, Lipase inhibition assay, HFD-fed obese rats	Adipogenesis, intracellular lipid content, expression of C/EBPβ, C/EBPα, SREBP-1c, FAS, LPL, aP2↓, expression of ATGL, HSL, SIRT1, p-AMPK in 3T3-L1 cells↑ Pancreatic lipase activity↓, AT fat mass, plasma TG, TC, LDL-C, AT TNF-α, p-NFκB↓, AT and muscle insulin signaling, p-Akt, GLUT4, adipoR1, IL-10↑	Liu et al. (2018), Liou et al. (2015), Hirata et al. (2015)
35. Lamiaceae				
Clerodendron glandulosum	Leaves (aqueous)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, leptin release, TG accumulation, GPDH↓, glycerol release↑ Lipid metabolism↑, lipogenesis↓, WAT mass, adipocyte size, serum lipids, FFAs, glucose, leptin↓, AT CPT1↑, AT PPARγ2, SREBP-1c, FAS↓	Jadeja et al. (2011)
Orthosiphon stamineus	Leaves (70% ethanol) Rosmarinic acid **104**	HFD-fed obese mice, obese diabetic rats	Lipid metabolism↑ Anti-oxidant activity↑, food intake↓, serum TG, TC, LDL-C, glucose, visceral fat mass, hepatic lipid content↓, hypothalamic POMC, hepatic SOD↑, hypothalamic NPY↓	Seyedan et al. (2017), Son et al. (2011)

Melissa officinalis	Leaves (aqueous-ethanol ext., ethyl acetate fr, ALS-L1023, ethanol ext.)	HFD-fed obese mice, human adipocytes	Lipid metabolism↑, Lipogenesis↓, Visceral AT mass, adipocyte size, MMP9, MMP2↓, hepatic CPT1, ACOX, MCAD, VLCAD, SOD2↑, serum TG, TC, FFAs, LDL-C, VLDL-C, liver TG, PPARγ, FAS, SREBP-1c, CD68, TNFα, MCP1, ICAM1, VCAM1↓, Human adipocytes PPARα, LXRα, PDK4↑, aP2, SCD1↓	Kim et al. (2017), Park et al. (2015a), Weidner et al. (2014)
Perilla frutescens	Leaves (50% ethanol, 70% ethanol), rosmarinic acid (**104**), isoegomaketone (**105**)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular TG content, GPDH release↓ Lipid metabolism and energy expenditure↑, epididymal fat mass, serum TG, TC, LDL, GOT, GPT, AT PPARγ, ACC, GPDH↓, AT adiponectin, ATGL, AT and liver AMPK, CPT1, PPARα, ACOX, HSL, UCP2, UCP3↑	Thomas et al. (2018), So et al. (2015), Kim and Kim (2009)
Rosmarinus officinalis (rosemary)	Leaves (methanol, fr enriched with rosmarinic acid or carnosic acid (**106**))	HepG2 cells, HFD-fed obese mice	Glycolysis and fatty acid oxidation↑, p-AMPK, p-ACC, PGC-1α, SIRT1, PPARγ↑, G6Pase↓ Epididymal fat mass, serum glucose, TG, TC, pancreatic lipase activity↓, PPARγ, fecal lipid excretion↑	Tu et al. (2013), Ibarra et al. (2010, 2011)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
36. Lauraceae				
Cinnamomum cassia	Cortex (water)	HFD-fed obese mice	Lipid metabolism and energy expenditure↑, food intake↓, hepatic, AT lipid mass, plasma lipids, glucose, adipocyte size↓, muscle MHC, PGC-1α, p-AMPK, p-ACC, NRF-1, Tfam↑	Song et al. (2017)
37. Lythraceae				
Lagerstroemia speciosa (banaba)	Leaves (hot water, ellagic acid rich fr)	3T3-L1 cells, Diabetic female KK-Ay mice	Adipogenesis, intracellular fat droplets, PPARγ, C/EBPα, SREBP-1c, FAS, HSL, ATGL, ACC↓ AT fat mass, hepatic TG content, serum glucose, HbA1c↓	Karsono et al. (2019), Suzuki et al. (1999)
Punica granatum (pomegranate)	Leaves	HFD-fed obese mice	Pancreatic lipase activity, food intake, AT fat mass, serum TG, TC, glucose↓	Lei et al. (2007)
38. Malvaceae				
Sida rhomboidea	Leaves (water)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular TG accumulation, leptin, GPDH↓, glycerol release↑ Epididymal fat mass, serum TG, TC, FFAs, and leptin, hepatic TG content, AT PPARγ2, SREBP-1c, FAS↓, AT CPT-1, lipid metabolism↑	Thounaojam et al. (2010, 2011)

39. Meliaceae				
Dysoxylum binectariferum	Stem-bark (ethanol ext., chloroform fr), rohitukine **107**	3T3-L1 cells, HFD-fed golden hamster	Adipogenesis, intracellular lipid accumulation, PPARγ, C/EBPα, aP2, FAS, GLUT4, p-Akt, MCE in adipocytes↓, Wnt3a, GATA2↑, hepatic lipogenesis↓, plasma TC, TG, LDL-C, hepatic TG content, expression of LDLR, HMGCR, SREBP2↓, hepatic LXRα↑	Varshney et al. (2014)
40. Moraceae				
Morus alba	Leaves (aqueous ethanol or fermented with *Cordyceps militaris*), 1-deoxynojirimycin (**108**), resveratrol (**47**)	HFD-fed obese mice	Lipid metabolism and energy expenditure↑, gut microbiota modulation, hepatic inflammation↓, serum TG, TC, LDL-C, hepatic TG content, inflammatory factors Nrf2, 4-HNE, HO-1, iNOS, COX2, p-JNK, lipogenic genes LXRα, SREBP-1c, C/EBPα, aP2, FAS, LPL↓, AT and liver PPARα, UCP1, UCP2, ATGL↑, Gut *Akkermansia*, *Bacteroidetes*↑, gut *Firmicutes*↓, fermented ext. autophagy genes beclin, LC3, Atg5↓, PI3K/Akt signaling↑	Lee et al. (2019c, 2020b), Sheng et al. (2019a), Ann et al. (2015)

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Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
41. Moringaceae				
Moringa oleifera	Leaves (70% ethanol)	HFD-fed obese rats	Energy expenditure, thyroid hormonal activity, and hepatic antioxidant activity↑, food intake↓, body fat mass, serum TG, TC, LDL-C, glucose, leptin, MDA, NO, protein carbonyls, GGT↓, Serum HDL-C, T3, T4, serum and hepatic GSH, GR, SOD, CAT↑, ghrelin secretion↓	Othman et al. (2019)
42. Nelumbonaceae				
Nelumbo nucifera	Leaves (ethanol), alkaloids, (6*R*, 6*aR*)-roemerine-N_{β}-oxide (**109**), liriodenine (**110**), pronuciferine (**111**), nuciferine (**112**); flavonoids, kaempferitrin (**113**), hyperoside (**114**), astragalin (**115**), quercetin (**23**)	Lipase enzyme inhibition assay, 3T3-L1 cells, HFD-fed obese mice	Pancreatic lipase activity, and adipogenesis↓, energy expenditure and lipid metabolism↑, hepatic inflammation↓, AT and liver fat mass, serum TG, TC, LDL-C, glucose, inflammatory cytokines IL-1β, IL-6, TNF-α, IFNγ↓, Serum HDL-C, hepatic AMPK, PPARα, CPT1, LPL, CYP7α1, IL-4, IL-10, muscle UCP3↑, hepatic PPARγ, C/EBPα↓	Wu et al. (2010, 2020b), Ma et al. (2015a), Ahn et al. (2013), Ono et al. (2006)
43. Pandanaceae				
Pandanus amaryllifolius (pandan)	Leaves (water)	HFD-fed obese mice	Central leptin sensitivity and insulin action in liver and muscle↑, plasma FG, leptin, TG, FFAs, hepatic lipid and TG content↓, plasma adiponectin, liver glycogen, muscle and AT GLUT4↑	Saenthaweesuk et al. (2016)

44. Piperaceae				
Piper nigrum	Seeds (water, ethyl acetate fr), piperonal (**116**)	HFD-fed obese rats	Lipid metabolism and thermogenesis↑, body fat mass, plasma glucose, insulin, TG, TC, LDL-C, leptin, MDA, TNFα, pancreatic lipase activity, expression of PPARγ, FAS, ACC, SREBP-1c, FAB4, HMGCR in liver and AT↓, AT adiponectin secretion, expression of hepatic GP_X, SOD, CAT, UCP2↑	Meriga et al. (2017), Parim et al. (2015)
P. nigrum and *P. longum*	Fruits (water), piperine (**117**)	HFD-fed obese rats	Lipid metabolism and energy expenditure↑, body fat mass, plasma TG, TC, LDL-C↓, plasma HDL-C, CNS MC-4R activity for energy expenditure↑	Shah et al. (2011)
45. Plantaginaceae				
Plantago lanceolata	Leaves (powder), acteoside (**118**), aucubin (**119**), catalpol (120)	HFD-fed obese mice	Lipid metabolism↑, visceral fat mass, serum glucose, TG, TC, FFAs, leptin, AT FAS↓, AT HSL, ADRD3, CPT2↑	Yoshida et al. (2013)

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Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
46. Poaceae				
Sasa quelpaertensis	Leaves (water), p-coumaric acid **19**	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid accumulation, SREBP-1c expression in 3T3-L1 cells↓, lipid metabolism and insulin action in mice↑, hepatic inflammation↓, liver and WAT fat mass, plasma TG, TC, GPT, GOT, LDH, expression of hepatic FAS, ACC, SCD1, TNFα↓, expression of adiponectin, p-AMPK, p-ACC, CPT-1α in AT, Nrf2, HO-1, PPARα, p-AMPK in liver↑	Park et al. (2020b), Kang et al. (2012a, 2013)
47. Polygonaceae				
Polygonum aviculare	Aerial parts (70% ethanol), myricitrin (**92**), avicularin (**121**), quercitrin (**122**), quercetin (**23**)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis and intracellular lipid accumulation in adipocytes↓, WAT fat mass, adipocyte size, plasma TG, leptin, MDA, expression of lipogenic genes SREBP-1c, PPARγ, FAS, aP2 in WAT and 3T3-L1 cells↓	Sung et al. (2013b)
P. multiflorum	Roots (ethanol), emodin (**123**), physcion (**124**), 2,3,5,4'-tetrahydroxystilbene-2-glucoside **125**	3T3-L1 cells, hepatic steatosis LO2 cells, HFD-fed obese mice	Adipogenesis↓, Lipolysis and lipid metabolism↑ In LO2 cells, TC, TG, DGAT1, HMGCR↓, HTGL, CYP7α1↑. Visceral fat mass, serum glucose, leptin, AT PPARγ, DGAT2↓, AT PPARα, CPT1, CPT2, UCP1, HSL↑. In 3T3-L1 cells, C/EBPα, PPARγ, FAS↓	Choi et al. (2018), Wang et al. (2014)

Rheum palmatum	Rhizomes (methanol), rhein (**126**)	HFD-fed obese mice	Energy expenditure↑, lipogenesis↓, WAT fat mass, plasma TG, TC, LDL-C, expression of PPARγ, LPL, aP2, CD36 in WAT, expression of FAS, ACC, ACOX in liver↓, expression of UCP1, UCP3, D2 in BAT↑	Zhang et al. (2012)
48. Orobanchaceae				
Rehmannia glutinosa	Roots (hot water), polysaccharides, polyphenols	HFD-fed obese mice	Lipid and glucose metabolism↑, gut microbiota modulation, body fat mass, WAT aP2↓, gut *Actinobacteria*, *Bifidobacterium*↑	Park et al. (2017b), Han et al. (2015b)
49. Oleaceae				
Ligustrum lucidum	Fruits (80% ethanol), 8*E*-nuzhenide (**127**)	HFD-fed obese mice	Lipid metabolism↑, WAT fat mass, plasma TG, ALT, AST, ALP, liver lipid content↓	Liu et al. (2014)
L. robustum	Leaves (water), phenylpropanoid glycosides	HFD-fed obese mice and rats	Lipid and glucose metabolism via modulation of gut microbiota↑, body fat mass, plasma glucose, TC, TG, LDL-C, leptin, AT DGAT, adipocyte size↓, hepatic CYP7α1, central leptin signaling↑, gut *Lactobacillus*, *Bacteroides*, *Bacilli, Bacteroidaceae*↑, gut *Firmicutes to Bacteroidetes* ratio, *Enterococcus*, *Clostridia*, *Clostridiales*, *Lachnospiraceae*↓	Zhou et al. (2019), Xie et al. (2015), Yang et al. (2015b)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
50. Ranunculaceae				
Coptis chinensis	Rhizomes (water, methanol ext., butanol fr), alkaloids, berberine (**48**), epiberberine (**128**), coptisine (**129**), palmatine (**130**), magnoflorine (**131**), polysaccharides	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid and TG accumulation, expression of PPARγ, C/EBPα in 3T3-L1 cells↓, lipid and glucose metabolism↑, plasma TG, TC, leptin, glucose, hepatic gluconeogenesis↓, muscle GLUT4, β-oxidation, glucose-oxidation, AMPK↑. Gut microbiota modulation Gut *Blautia*, *Allobaculum*, fecal SCFAs↑	Choi et al. (2014), Zhang et al. (2014b), Jiang et al. (2013)
51. Rutaceae				
Aegle marmelos (bael)	Leaves (methanol, dichloromethane fr), umbelliferone (**132**), esculetin (**133**), (3,3-dimethylallyl)-halfordinol (**134**)	3T3-L1 cells, HFFD-fed obese mice	Adipogenesis, intracellular lipid accumulation in 3T3-L1 cells↓, visceral fat mass, plasma glucose, insulin, TG, TC, expression of PPARγ, C/EBPα in WAT↓, plasma adiponectin, expression of PPARα, GLUT4 in WAT and muscle↑	Saravanan et al. (2014), Karmase et al. (2013a, 2013b)
Citrus depressa	Fruits (methanol), nobiletin (**135**), tangeritin (**136**)	HFD-fed obese mice	Lipid metabolism↑, inflammation↓, WAT fat mass, plasma TG, leptin, expression of SCD1, aP2, DGAT1, TNFα, MCP-1 in AT↓, expression of p-Akt, PPARα, CPT1, UCP2↑	Lee et al. (2011b, 2013b)

Citrus × *sinensis* (moro blood orange)	Fruit-juice, cyanidin-3-glucoside (**31**)	HFD-fed obese mice	Lipid metabolism↑, Hepatic lipid content, serum TG, TC, ALT, expression of hepatic LXRα, FAS, HMGCR, GPAT1↓, expression of hepatic PPARα, ACOX↑	Salamone et al. (2012)
Evodia rutaecarpa	Fruits (ethanol), evodiamine (**137**)	HFD-fed obese rats	Lipid metabolism↑, epididymal fat mass, serum FFAs, hepatic TG and lipids content↓	Kobayashi et al. (2001)
Murraya koenigii (curry leaves)	Leaves (ethanol, ethyl acetate fr), mahanimbine (**138**)	HFD-fed obese rats	Lipolysis↑, body fat mass, plasma glucose, TG, TC↓	Birari et al. (2010)
52. Rubiaceae				
Cinchona officinalis	Bark (methanol), cinchonine (**139**)	HFD-fed obese mice	Lipogenesis and inflammation↓, epididymal fat mass, plasma TG, TC, hepatic TG, TC, expression of TLR2, TLR4, MyD88, TNFα, IL-6, IFNα, GalR, C/EBPα, PPARγ2, SREBP-1c, aP2, LPL, leptin in AT, expression of FoxO1 in liver↓, AT Wnt signaling, Wnt10b↑	Jung et al. (2012c)
Morinda citrifolia (noni)	Fruit-juice, polysaccharides, iridoids, polyphenolics; leaves (60% ethanol)	HFCD-fed hamsters, HFD-fed obese mice	Lipid and glucose metabolism, antioxidant activity↑, plasma TG, TC, MDA, glucose, insulin, liver lipid mass, expression of hepatic SREBP-1c, FoxO1, PEPCK, G6Pase↓, expression of hepatic PPARα, UCP2, GSH, fecal lipid excretion↑	Lin et al. (2012), Nerurkar et al. (2012), Jambocus et al. (2016)

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Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
53. Sapindaceae				
Aesculus turbinata	Seeds (aqueous ethanol, butanol fr) escins, escin Ib (**140**), escin IIa (**141**), proanthocyanidins	Lipase inhibition assay, HFD-fed obese mice	Pancreatic lipase activity↓, WAT fat mass, serum TG, TC, glucose, hepatic TG, lipid content↓, fecal lipid excretion↑	Kimura et al. (2006, 2008, 2011), Hu et al. (2008)
54. Solanaceae				
Capsicum annuum, C. frutescens (hot peppers)	Seeds (methanol, capsicoside G (**142**) rich fr), capsaicin (**49**), dihydrocapsaicin (**144**)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid content, expression of C/EBPα, PPARγ, SREBP-1c in 3T3-L1 cells↓, lipid metabolism and energy expenditure in mice↑, Inflammation↓, epididymal fat mass, serum lipids, hepatic TG, lipid content, expression of PPARγ, C/EBPα, SREBP-1c, FAS, FABP4, TNFα, IL-6, MCP-1, CD68 in AT and liver↓, expression of HSL, PPARα, PGC-1α, CPT-1α, adiponectin, UCP2 in AT and liver↑ Lipid metabolism↑	Sung et al. (2016), Lee et al. (2011a), Jeon et al. (2010), Kang et al. (2010b)
Solanum lycopersicum	Green fruits (water), α-tomatine (**145**), dehydrotomatine (**146**)	HFD-fed obese mice	Epididymal and live fat mass, serum TG, TC, LDL-C, hepatic TG, TC content, expression of HMGCR, C/EBPα, PPARγ, AT perlipin↓, liver p-AMPK, p-ACC↑	Choi et al. (2013)

55. Saxifragaceae				
Bergenia crassifolia	Leaves (fermented), bergenin (**147**), arbutin (**148**)	HFD-fed obese rats	Lipogenesis and food intake↓, body fat mass, serum TG, glucose↓	Shikov et al. (2012)
56. Theaceae				
Camellia sinensis	Leaves (water), flower-buds (methanol), EGCG **35**, chakasaponin-II **149**	HFD-fed obese rats, HFD-fed obese TSOD mice	Lipid metabolism, energy expenditure and food intake↓, visceral fat mass, plasma TG, TC, LDL-C, leptin, FFAs, AST, ALT, hypothalamic NPY expression↓, plasma HDL-C, hypothalamic serotonin expression, AT PGC-1α, PPARγ, CPT-1, adiponectin, UCP-1, CIDEA, PRDM-16 expression↑	Chen et al. (2017), Hamao et al. (2011)
57. Ulmaceae				
Holoptelea integrifolia	Bark (methanol)	HFD-fed obese rats	Lipogenesis↓, plasma lipids, apoB, hepatic HMGR↓, plasma HDL-C, apoA1, LCAT, fecal lipid excretion↑	Subash and Augustine (2013)
58. Vitaceae				
Vitis vinifera	Seeds (commercial ext.), proanthocyanidins, resveratrol (**47**)	HFD-fed obese mice	Lipid metabolism and energy expenditure↑, AT inflammation↓, epididymal and back fat mass, serum and hepatic TG, TC, ACC, AT iNOS, TNFα, IL-1β, IL-6, leptin↓, hepatic CPT-1, BAT UCP-1, serum HDL-C↑	Park et al. (2008), Mahanna et al. (2019)

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Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
Vitis thunbergii var. *taiwaniana*	Roots (aqueous ethanol or hot water), ε-viniferin **150**	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, expression of HMGCR in 3T3-L1 cells↓, lipid and energy expenditure in mice↑ Epididymal and liver fat mass, serum leptin, glucose, insulin, TC, LDL-C, GOT, expression of hepatic SREBP-1, PPARγ↓, expression of hepatic p-AMPK, CPT1↑	Lu et al. (2017), Hsu et al. (2014)
59. Zingiberaceae				
Alpinia officinarum	Rhizomes (ethanol), galangin **151**	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid content, expression of PPARγ, C/EBPα, SREBP-1c in 3T3-L1 cells↓, lipogenesis, body fat mass, serum lipids, glucose, insulin, leptin, expression of FAS, C/EBPα, PPARγ, SREBP-1c in liver and AT of mice↓	Jung et al. (2012a)
Aframomum melegueta	Seeds (ethanol or methanol), 6-paradol (**152**), 6-shogaol (**153**), 6-gingerol (**154**)	HFD-fed obese mice, Obese men, Lipase inhibition assay	Energy expenditure and antioxidant activity↑, body fat mass, hepatic TG, TC, MDA↓, hepatic SOD, CAT, GP_X, GSH, BAT UCP-1, TRPV1 signaling↑, fecal lipid excretion↑ Pancreatic lipase activity↓	Hattori et al. (2017), Adigun et al. (2016), Sujita et al. (2013), Ekanem et al. (2007)

Boesenbergia pandurata	Rhizomes (ethanol), panduratin A **155**	3T3-L1 cells, HepG2 cells, L6 cells, HFD-fed obese mice	Adipogenesis, hepatogenesis↓, lipid metabolism↑, hepatic and AT fat mass, serum TC, TG, LDL-C, liver TG content↓, expression of ACC, FAS, PPARγ, SREBP-1c↓, expression of p-AMPK, PPARα, PGC-1α, CPT-1, UCP-1, UCP-2 in WAT, liver, 3T3-L1 and HepG2 cells↑, expression of p-AMPK, PGC-1α, SIRt1, NRF-1, Tfam, ERRα in L6 cells↑	Kim et al. (2012a, 2016a)
Curcuma longa	Rhizomes (ethanol ext., hexane and ethanol fr or 50% ethanol ext. fermented with *Aspergillus oryzae,* curcuminoids (curcumin (**9**), desmethoxycurcumin (**156**), bisdesmethoxycurcumin (**157**))	3T3-L1 cells, HFD-fed obese mice or rats, human subcutaneous AT (h-SAT) culture	Adipogenesis and lipogenesis↓, lipid and energy metabolism↑, body fat mass, plasma TG, TC, VLDL, hepatic TG, expression of ACC, PPARγ, C/EBPα, FAS, aP2, LPL in AT↓, expression of HSL, ATGL, adiponectin, CPT-1, p-AMPK in AT, ACOX in liver↑, leptin secretion in h-SAT↓	Al-Lahham et al. (2017), Kim et al. (2016), Ejaz et al. (2009), Asai and Miyazawa (2001)

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Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
Zingiber officinale	Rhizomes (95% ethanol or hot water), 6-gingerol (**154**), 6-shogaol (**153**)	3T3-L1 cells, human myotube culture, HFD-fed obese rats or mice, HFrucD-fed obese NAFLD rats	Adipogenesis, intracellular lipid content in 3T3-L1 cells↓, mitochondrial biogenesis in human myotubes↑, lipid metabolism in mice↑, lipid synthesis, oxidative stress and inflammation↓, body fat mass, hepatic TG content, plasma glucose, insulin, TG, TC, PL, LDL-C, FFAs↓, liver and AT TNF-α, MCP-1, IL-6, ACC, FAS, SCD1, aP2, PPARγ↓, hepatic HMGCR, CYP2E1, ChREBP, LPL, G6Pase↓, hepatic HO-1, SOD, GP_X, NRF1/2, FGF21, p-AMPK, CPT1, ACOX1, PGC1α↑, AMPK/PGC1α signaling in muscle, liver and BAT↑, expression of miR-21, miR-132, related to inflammation in WAT↓	Seo et al. (2021), Deng et al. (2019b), Kim et al. (2018b), Lai et al. (2016), Misawa et al. (2015), Li et al. (2014a), Gao et al. (2012), Nammi et al. (2009)
B. Dietary seaweeds (marine algae) (Brown/green/red algae family and species)				
1. Alariaceae				
Undaria pinnatifida (brown)	Ethanol ext. or dry powder, fucoxanthin (**158**), fucoidan (**159**) (sulfated polysaccharide)	3T3-L1 cells, HFD-fed obese rats	Adipogenesis, intracellular lipid content, expression of adipogenic and inflammation related genes PPARγ,	Grasa-Lopez et al. (2016), Kim and Lee (2012)

			C/EBPα, aP2, TNF-α, MCP-1, PAI-1 in 3T3-L1 cells↓, lipid metabolism and thermogenesis in rats↑, lipogenesis↓, WAT and liver fat mass, serum glucose, insulin, TG, TC, leptin, LDL/VLDL-C, CRP, hepatic ACC↓, expression of PPARα, PGC-1α, UCP-1 in WAT and liver↑	
2. Caulerpaceae				
Caulerpa okamurae (green)	Ethanol ext.	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid content, expression of PPARγ, C/EBPα, SREBP-1c in 3T3-L1 cells↓, lipogenesis in mice↓, plasma TG, TC, FFAs, WAT fat mass, expression of PPARγ, C/EBPα, SREBP-1c, FAS, ACC, CD36 in WAT↓	Sharma et al. (2017)
C. taxifolia	Methanol/ethyl acetate ext., caulerpenyne (**160**)	Lipase inhibition assay	Pancreatic lipase activity inhibited (IC_{50} of 13 μM against 4-MU oleate)	Bitou et al. (1999)
3. Codiaceae				
Codium cylindricum (green)	Powder, siphonaxanthin (**161**)	HFD-fed obese mice, HepG2 cells	Lipid metabolism in mice↑, lipogenesis↓, perirenal fat mass, expression of SREBP-1c, FAS, SCD1, PPARγ, GPDH in WAT↓, expression of CPT-1α, PGC-1α, ACOX1 in WAT↑, Nrf2 and its target genes in HepG2 cells↑	Li et al. (2018b), Zheng et al. (2020)

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Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
C. fragile	70% ethanol ext., sulfated polysaccharide	HFD-fed obese mice	Modulation of gut microbiota composition, relative abundance of bacteria of family, *Acetatifactor*, *Ruminococcaceae*, *Lachnospiraceae*, related to SCFA production↑	Kim et al. (2020)
4. Ishigeaceae				
Ishige okamurae (brown)	50% ethanol ext., fucoxanthin (**158**), diphlorethohydroxycarmalol (**162**)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid droplets, expression of C/EBPα, PPARγ↓, p-HSL, ATGL, p-AMPK in 3T3-L1 cells↑, lipid metabolism↑, lipogenesis in mice↓, abdominal fat mass, serum FG ang PPG, TC, LDL-C, ALT, AST, LDH, expression of DGAT1, FAS, SREBP-1c in liver↓, expression of hepatic and WAT p-AMPKα, CPT-1, WAT ATGL, HSL↑	Ding et al. (2019), Seo et al. (2018)
5. Lessoniaceae				
Ecklonia cava (brown)	70% ethanol ext., ethyl acetate fr or water ext., dieckol (**163**) enriched fr, phlorotannins, phloroglucinol, eckol **164**, dieckol, 8,8'-bieckol **165**	HFD-fed obese male mice, Lipase inhibition assay	Lipid metabolism and antioxidant activity in mice↑, lipogenesis and inflammation in mice↓, Body fat mass, plasma leptin, TG, TC, LDL-C, 4-HNE, hepatic TG content, expression of SREBP-	Eo et al. (2015, 2017), Park et al. (2015b), Kim et al. (2012c)

			1c, FAS, ACC, LPL, NF-κB, IL-1β, TNF-α, MCP-1, FXR, SHP, MDA in liver↓, expression of hepatic CAT, GP_X, p-AMPK, SIRT1, CYP7α1, HNF-4α↑, expression of renal NLRP3 inflammasome, NF-κB, MCP-1, TNFα, CRP↓, pancreatic lipase activity↓	
E. stolonifera	Ethanol ext., ethyl acetate fr or methanol ext., dichloromethane fr, fucosterol (**166**) and phlorotannins, eckol, dieckol, phlorofucofuroeckol A **167**	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid content, expression of SREBP1, PPARγ, C/EBPα, lipin1, DGAT1 in 3T3-L1 cells↓, lipid catabolism, lipolysis and thermogenesis in mice↑, AT and hepatic lipid mass, serum TC, TG, LDL-C↓, expression of CPT1, UCP1, PRDM16, p-HSL, ATGL, MGL in WAT↑, expression of C/EBPα, PPARγ, FABP4 in WAT↓	Jin et al. (2020), Jung et al. (2014a, 2014b), Yoon et al. (2008)
6. Laminariaceae				
Laminaria japonica (brown)	Ethanol ext., fucoxanthin (**158**)	HFD-fed obese rats	Lipid metabolism and thermogenesis↑, lipogenesis↓, AT fat pad mass, adipocyte size, serum glucose, insulin, leptin, TG, TC, LDL-C, FFAs, TNF-α, GOT, expression of SREBP-1c, ACC, FAS, PPARγ, SCD1, GPAT,	Jang and Choung (2013)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
			AGPAT, DGAT, LPL in WAT and liver↓, expression of hepatic p-AMPK, p-ACC, PPARα, CPT1↑, expression of ATGL, HSL, CPT1 in WAT↑, expression of PPARα, ACOX, CPT1, UCP2, UCP3 in muscle↑	
7. Halymeniaceae				
Grateloupia elliptica (red)	60% ethanol ext	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid content, expression of PPARγ, SREBP-1c, FABP4 in 3T3-L1 cells↓, thermogenesis↑, lipogenesis in mice↓, WAT fat mass, adipocyte size, serum TG, TC, leptin, expression of C/EBPα, SREBP-1c, PPARγ in WAT↓, expression of FGF21 in WAT, UCP1, UCP3 in BAT↑	Lee et al. (2020a)
8. Gelidiaceae				
Gelidium amansii (red)	Ethanol ext., hot water ext., sulfated polysaccharide	3T3-L1 cells, HFD-fed obese mice, HFD-fed hamsters	Adipogenesis, intracellular lipid content, expression of PPARγ, C/EBPα, SREBP-1c in 3T3-L1 cells↓, lipogenesis in mice↓, AT fat mass, adipocyte size, serum TG, TC, LDL-C, FFAs, expression of PPARγ, SREBP-1c, C/EBPα	Kang et al. (2016, 2017), Park et al. (2017a), Yang et al. (2017b)

			in WAT of mice↓, expression of hepatic SREBP1, SREBP2, FAS in hamsters↓, serum HDL-C, expression of adiponectin, HSL, p-AMPK in WAT↑, fecal lipids and bile acid excretion, hepatic p-AMPK expression in hamsters↑	
9. Plocamiaceae				
Plocamium telfairiae (red)	40% ethanol	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid droplets accumulation, expression of PPARγ, SREBP1, ACC, C/EBPα in 3T3-L1 cells↓, Thermogenesis in mice↑, WAT fat mass, serum TG, TC, insulin↓, expression of UCP1, UCP3 in BAT↑	Lu et al. (2020)
10. Sargassaceae				
Sargassum polycystum (brown)	Powder, fucoxanthin, fucoidan, high Ca content	HFD-fed obese rats	Thermogenesis, antioxidant activity, lipid metabolism and lipolysis↑, body fat mass, plasma TG, TC↓, plasma HDL-C, SOD, GP_X↑, fecal lipids excretion↑	Awang et al. (2014), Matanjun et al. (2010)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
11. Scytosiphonaceae				
Petalonia binghamiae (brown)	Ethanol ext., fucoxanthin (**158**)	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular lipid droplets, expression of C/EBPα, PPARγ, SREBP-1c, aP2 in 3T3-L1 cells↓, expression of p-AMPK, p-ACC in 3T3-L1 cells↑, lipid oxidation in mice↑, AT fat mass, liver lipid droplets, serum TG, GPT, GOT↓, expression of p-AMPK, p-ACC in WAT↑	Kang et al. (2010c, 2012b)
12. Hematococcaceae				
Haematococcus pluvialis (micro green alga)	Ethanol ext., astaxanthin (**168**)	HFD-fed obese mice, HF-HFrucD-fed obese mice, oerweight and obese adults	Lipid synthesis and oxidative stress↓, WAT and liver fat mass, plasma TG, TC, FFAs, MDA, ISP, hepatic TG content, AST, ALT, TGF-β1, CYP2E1, MPO↓, plasma and hepatic CAT, SOD, GP_X, GST, TAC↑	Bhuvaneswari et al. (2010), Ikeuchi et al. (2007), Choi et al. (2011)
C. Fungi (fruiting bodies or mycelia of macrofungi mushrooms and others microfungi). Family and species				
1. Auriculariaceae				
Auricularia polytricha (edible mushroom grows in trees)	Water ext., polysaccharides	HFD-fed NAFLD rats or STZ-diabetic mice	Lipogenesis, inflammation and oxidative stress↓, hepatic fat mass, plasma and hepatic TG, TC, FFAs, ALT, TNF-α, IL-6, MDA↓, plasma HDL-C, hepatic SOD, GP_X, GR↑	Chiu et al. (2014), Xiang et al. (2021)

A. auricular-judae (medicinal mushroom)	70% ethanol ext.	3T3-L1 cells, HFD-fed obese mice	Adipogenesis, intracellular TG content, expression of adipogenic genes, PPARγ, C/EBPα, FAS in 3T3-L1 cells↓, lipolysis and lipid metabolism in mice↑, lipogenesis↓, serum lipids, hepatic fat mass, expression of lipogenic genes↓	Reza et al. (2015)
2. Ganodermataceae				
Ganoderma lucidum (medicinal mushroom)	Water ext., polysaccharides	HFD-fed obese mice	Gut dysbiosis and inflammation in metabolic tissues↓, body fat mass, hepatic and WAT TNF-α, IL-6, IL-1β, PAI-1, MCP-1, p-JNK, serum LPS, TLR4↓, hepatic and WAT IL-10, p-Akt↑, relative abundance of gut bacterial spp. of *Eubacterium*, *Roseburia*, *Clostridium*↑, relative abundance of *Escherichia*, *Enterococcus*, *Lactococcus*, *Mucispirillum* spp. in gut↓	Chang et al. (2015)
3. Meripilaceae				
Grifola frondosa (edible mushroom grows on oak trees)	Ethanol ext. of mycelia, polysaccharides	HFD-fed obese mice, HFD-fed obese rats, C2C12 cells-exposed to high palmitate	Lipid and energy metabolism↑, Gut dysbiosis↓, body fat mass, plasma TC, TG, leptin, hepatic TG content, expression of SREBP-1c, LPL, FAS, C/EBPα, FABP4 in liver and WAT↓, expression of	Aoki et al. (2018), Li et al. (2019)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
			PPARδ target genes, PDK4, CPT-1β, PGC-1α, ACSL3, UCP3, GLUT4 in muscle of mice↑, expression of PPARδ, PDK4, p-AMPK, p-Akt in C2C12 cells↑, expression of hepatic CYP7A1, BSEP in rats↑, relative abundance of gut bacterial spp. of *Clostridium* XVIII, *Butyricicoccus*, *Turicibacter*↓, bacterial spp of *Ruminococcus*, *Helicobacter*, *Barnesiella*, *Paraprevotella*, *Intestinimonas* in the gut↑	
4. Mycenaceae				
Panellus serotinus	Water ext.	Leptin-deficient obese diabetic mice	Lipid metabolism↑, serum TG, TC, LDL-C, AST, ALT, hepatic TG, TC content, FAS activity↓, serum adiponectin↑	Inoue et al. (2013)
5. Omphalotaceae				
Lentinus edodes (edible mushroom)	Powder, eritadenine (**187**), β-glucans	HFD-fed obese mice and rats	Lipid metabolism↑, abdominal fat mass, serum TC, TG, LDL-C↓, expression of hepatic CYP7A1↑	Yang et al. (2013), Handayani et al. (2011)

6. Physalacriaceae				
Flammulina velutipes (edible mushroom)	Water ext., polysaccharides fr	HFD-fed obese mice	Lipolysis↑, fat absorption↓, hepatic lipid content, serum TC, TG, LDL-C, GOT, GPT, LDH↓, serum HDL-C, fecal lipid excretion↑, gut *Firmicutes* to *Bacteroidetes* ratio↓, relative abundance of gut immunity improving bacteria, *Porphyromonadaceae*, *Bacteroidaceae* spp.↑, relative abundance of gut *Lactobacillaceae*, *Lachnospiraceae*↓	Miyazawa et al. (2018), Zhao et al. (2019)
7. Polyporaceae				
Pleurotus citrinopileatus	Water ext., polysaccharides, phenolics	HFD-fed obese mice	Lipogenesis and food intake↓, body fat mass, serum TG, TC, LDL-C, NEFAs, AST, LDH↓, serum HDL-C↑	Sheng et al. (2019b)
P. sajor-caju	Water ext., β-glycan rich fr	HFD-fed obese mice	Lipolysis and antioxidant activity↑, inflammation↓, WAT and liver fat mass, serum TG, TC, LDL-C, glucose, MDA, ALT, AST, ALP, expression of WAT NF-κB, TNF-α, IL-6, MCP-1, PPARγ, SREBP-1c, LPL↓, expression of adiponectin, HSL, ATGL in WAT, of SOD, CAT, GP_X in the liver and kidney↑	Kanagasabapathy et al. (2012, 2013)

(continued)

Table 4.1 (continued)

Family, Plant species	Active extract/active component	Experimental model	Major activity and molecular targets	References
P. ostreatus (edible mushroom)	DMSO ext., anthraquinones	3T3-L1 cells	Adipogenesis, intracellular lipid content, expression of C/EBPα, PPARγ, FAS, ACS, SREBP-1c, FABP4↓	Bindhu and Das (2019)
8. Tremellaceae				
Tremella fuciformis	Water ext., polysaccharides	3T3-L1 cells	Adipogenesis, intracellular TG content, expression of adipogenic-related genes, PPARγ, C/EBPα, leptin↓	Jeong et al. (2008)
D. Dietary marine fishes (family and species)				
1. Euphausiidae				
Euphausia superba (Antarctic krill)	Acetone-ethanol (1:1) ext., n-3-PUFA, eicosapentaenoic acid (**169**), docosahexaenoic acid (**170**)	HFD-fed obese mice	Lipid and glucose metabolism↑, insulin sensitivity↑, plasma TC, glucose, hepatic fat mass, TG, TC, expression of FAS, ACC, SCD1, MGL, SREBP-1c, SREBP2, HMGCR, LDL-R, HSL, TNF-α↓, plasma adiponectin↑	Gigliotti et al. (2011), Tandy et al. (2009)
E. Marine sponges (family and species)				
1. Hymedesmiidae				
Phorbas spp.	Phorbaketal A (sesterpenoid) (**170a**)	3T3-L1-adipocytes	Adipogenesis and adipogenic genes expression↓	Byun et al. (2013)

4.5.3 Stimulatory Effect on Energy Expenditure

White adipose tissue (WAT) is the main "storage site" of excess energy in obese humans, primarily in the form of triglycerides (TG) (fat). Therefore, stimulation of energy expenditure via lipolysis of TG into free fatty acids (FFAs) and glycerol and their mobilization to the energy-demanding tissues, liver, and skeletal muscles for FA oxidation is an important therapeutic target in prevention of obesity. The stimulation of energy expenditure may be regulated centrally via regulation of thermogenic markers, melanocortin receptor (MCR), melanin-concentrating hormone, and leptin signaling in suppression of food intake (Spiegelman and Flier 2001) and peripherally by promoting lipolysis and FA oxidation in the AT, liver, and skeletal muscle via upregulation of AMPK activation. Insulin acts as lipolytic inhibitor via its insulin receptors, while catecholamines (adrenaline and noradrenaline) and natriuretic peptide promote lipolysis by upregulation of the activity of two main lipolytic enzymes, hormone sensitive lipase (HSL), and adipose triglyceride lipase (ATGL) in human WAT. AMP-activated protein kinase (AMPK), a phosphorylating enzyme on activation (phosphorylation), stimulates the phosphorylation of HSL, which in turn increases the phosphorylation of ACC to suppress lipogenesis in metabolic tissues. Accumulating evidence demonstrates that activated AMPK stimulates hepatic FA oxidation (FAO) and ketogenesis; inhibits hepatic cholesterol and TG synthesis, and lipogenesis; stimulates FAO and glucose uptake in skeletal muscle; and stimulates thermogenesis and inhibits lipogenesis in BAT and WAT (Zimmermann et al. 2004; Sengenes et al. 2000; Langin 2006; Yuliana et al. 2014). Brown adipose tissue (BAT) within WAT, on activation is able to disperse stored energy as heat by non-shivering thermogenesis process. Brown adipocytes on activation by sirtuin-1 (SIRT-1) or AMPK or adrenergic receptor-beta 3 (ADRB3 or β3-AR) or heat shock factor-1 (HSF-1) upregulate the expression levels of heat producing mitochondrial membrane proteins, uncoupling protein-1 (UCP-1) and other proteins including Cidea, PR-domain containing protein 16 (PRDM-16), and Cox-7α1 through peroxisome proliferator-activated receptor gamma (PPARγ) deacetylation and PPARγ-coactivator 1α (PGC-1α) activation to produce heat and thermogenic "brown-like" cells (beige cells). Upregulation of deiodinase-2 (DIO2) increases the expression of thyroid hormone T3, which in turn activates β3-adrenergic receptor to increase UCP1 gene expression for browning of WAT. Stress kinase MEK promotes translocation of HSF-1 to nucleus for transcriptional activation of PGC-1α for energy expenditure. Therefore, promoting WAT browning and BAT activation is a potential therapeutic approach to combat obesity (Kurylowicz and Puzianowska-Kuznicka 2020; Volke and Krause 2020; Fischer et al. 2019; Wu et al. 2018; Tang et al. 2015; Qiang et al. 2012). Several phytochemicals including resveratrol (**47**) (Fig. 4.1), berberine (**48**), curcumin (**9**), capsaicin (**49**), cryptotanshinone (**452**) from *Salvia miltiorrhiza*, fucoxanthin (**158**) from seaweed *Undaria pinnatifida*, and green tea catechins, theaflavins, and caffeine **41** have been reported to stimulate lipolysis, FAO, and mitochondrial biogenesis and thermogenesis processes via activation of SIRT1, AMPK, β3-AR, and other pathways in treatment of obesity in animal models (Table 4.1).

4.5.4 Inhibition of Adipogenesis

Adipocytes play a central role in the maintenance of lipid homeostasis and energy balance in the body of humans by storing triglycerides or releasing free fatty acids (FFAs) in response to changes in energy demands. In obese humans, the adipose tissue is increased abnormally due to both hyperplasia (increased number of cells) and hypertrophy (increased size) of adipocytes by the process of maturation (cell growth) of preadipocytes and differentiation of mature adipocytes, known as adipogenesis. Therefore, inhibition of adipogenesis is considered as a promising therapeutic target for treatment of obesity and diabetes. In cellular model, mouse cell line, 3T3-L1 preadipocytes are commonly used for the study of obesity in vitro, because such cells accumulate triglycerides for differentiation in the maturity stage on culture under pro-differentiation cocktail stimulators, such as insulin, IBMX (3-isobutyl-1-methylxanthine), fetal bovine serum, dexamethasone, glucocorticoids, and thyroid hormone. A wealth of observations demonstrates that adipocyte differentiation of embryonic stem cells and 3T3-L1 preadipocytes occurs in four main stages, namely, growth arrest, mitotic clonal expansion (replication of DNA and duplication of cells), early differentiation, and terminal differentiation. At the growth arrest stage, preadipocytes induce the expression of early markers of differentiation, namely, C/EBPβ and C/EBPδ in response to hormonal stimulation. In mitotic clonal expansion (MCE) stage, C/EBPβ alone or in combination with C/EBPδ on activation induces the expression of adipocyte-specific genes, PPARγ, and CCAAT/enhancer binding protein-alpha (C/EBPα) and their target genes, sterol regulatory element binding protein-1c (SREBP-1c), fatty acid synthase (FAS), adipocyte binding protein 2 (aP2), stearoyl CoA desaturase-1 (SCD-1), acyl CoA oxidase (ACOX), phosphoenol pyruvate carboxykinase (PEPCK), glucose transporter-4 (GLUT-4), and lipoprotein lipase (LPL) via induction of MAPK cascade (increased phosphorylation of ERK1/2 and JNK kinases) by extracellular leukemia inhibitory factor (LIF) and its receptor (Wu et al. 1999). The MCE is considered as a prerequisite for differentiation of preadipocytes into adipocytes, because at this stage, preadipocytes increase DNA synthesis and double its cell number. Moreover, in this stage, C/EBPβ increases the expression of various cyclins, namely, cyclins A, B, D, and E, and cyclin-dependent kinases (CDKs), such as CDK-4, -2, and -1 for regulation of cell cycle process (Tang et al. 2003). Kruppel-like factor 4 (KLF-4) plays a significant role on directly binding to C/EBPβ promoter region and, in combination with early growth response protein (EGR2), also known as Krox20, induces the expression of PPARγ and C/EBPα, the main transcription factors of adipogenesis (Birsoy et al. 2008). A recent study demonstrates that C/EBPβ recruits epigenetic lysine methyltransferases, MLL3 and MLL4 for activation of bromodomain-containing protein 4 (BRD4), which induces Pol II for activation and upregulation of the expression of PPARγ and C/EBPα in obese mice (Lee et al. 2017a, 2019a). The cell cycle is closely associated with adipocyte cell growth and proliferation. A wide variety of phytochemicals (listed in Table 4.1) have been reported to inhibit adipogenesis of preadipocytes or to induce apoptosis of mature adipocytes by suppression of the expression of PPARγ and C/EBPα, key transcription factors for

adipogenesis by targeting different stages of adipocyte cell growth through cell cycle arrest in mitotic clonal expansion stages via suppression of MAPK/ERK phosphorylation, inhibition of FoxO1 signaling pathway, or induction of Wnt signaling and AMPK activation. AMPK activation induces G1 cell cycle arrest by decreasing the levels of cell growth proteins, cyclin A, cyclin D1, and phosphorylated-retinoblastoma (pRb) and increasing the expression of negative regulators of adipogenesis, CCAAT/enhancer-binding protein (C/EBP), homologous protein (CHOP), and Kruppel-like factor-2 (KLF-2). Some review articles highlighted the potentials of the phytochemicals in treatment of obesity via inhibition of adipogenesis at different stages of adipocyte cell growth and in mature adipocytes (Chang and Kim 2019; Rayalam et al. 2008; Kim et al. 2006; Rosen et al. 2000). However, a research finding demonstrates that the inhibition of adipogenesis or adipose tissue expansion is unhealthy because intracellular triglycerides removal rate from adipocytes is positively correlated with increased lipolysis (by mainly hormone-sensitive lipase (HSL)) leads to increased FFAs levels and development of dyslipidemia and insulin resistance in the body, which in turn, contribute to high risk factors for diabetes and cardiovascular complications (Arner et al. 2011).

4.5.5 Regulation of Lipid Metabolism via PPARα Activation

The reduction of fat stores by hydrolysis of accumulated triglycerides (TG) in the peripheral liver, adipose tissue, and skeletal muscle is one of the strategies to combat obesity. Obesity-related chronic inflammation increases the lipolytic release of free fatty acids (FFAs) from adipose tissue fat and raises plasma FFAs levels that are subsequently stored mainly in the liver as TGs and develops nonalcoholic fatty liver disease (NAFLD). In addition, accumulation of FFAs in other metabolic tissues, skeletal muscle, heart, and kidney causes insulin resistance. Moreover, obesity-related dyslipidemia results in the development of cardiovascular diseases (CVDs). Several studies demonstrate that in skeletal muscle of obese individuals, fatty acid oxidation is decreased due to low levels of CPT-1, citrate synthase, and cytochrome C oxidase because of intramuscular lipid accumulation, particularly in the cystol of skeletal muscle and thereby resulting in insulin resistance in myotubes. Peroxisome proliferator-activated receptor alpha (PPARα), a ligand-activated transcription factor of steroid hormone receptor subfamily and nuclear receptor, is highly expressed in the liver, skeletal muscle, brown adipose tissue, and heart for fatty acid oxidation in healthy nonobese humans. PPARα regulates the expression of a number of genes for lipid and lipoprotein metabolism for reduction of plasma and hepatic TGs levels and plasma small dense low-density lipoprotein (LDL) particles and enhancement of high-density lipoprotein cholesterol (HDL-C) levels. PPARα stimulates the transcription of genes critical for fatty acid oxidation (FAO) and ketogenesis in both humans and rodents and promotes gluconeogenesis only in rodents through upregulation of PGC-1α and HNF-α. Estrogen has been found to inhibit the actions of PPARα on obesity and lipid metabolism and hence PPARα is not effective in obese men and obese postmenopausal women in obesity management. Possibly,

17β-estradiol inhibits the activity of PPARα by inhibition of the recruitment of PPARα coactivator CREB-binding protein in premenopausal women because of ovarian factor. Synthetic PPARα agonists, such as fibrates, namely, fenofibrate (**50**) and ciprofibrate (**51**), used for treatment of dyslipidemia, have been shown to reduce the symptoms of obesity in animal models by both increasing hepatic fatty acid oxidation (FAO) and decreasing the levels of plasma and hepatic TGs levels by activation of PPARα gene in the liver. The transcription factor PPARα on activation recognizes the natural lipid ligands FA derivatives and binds them to PPAR response elements (PPREs) located in the regulatory regions of its target genes and upregulates the expression of peroxisomal β-oxidation related genes, such as acyl-CoA oxidase 1 (ACOX1) and mitochondrial β-oxidation-related genes, such as carnitine palmitoyltransferase 1 (CPT 1), CPT 2, medium-chain acyl-CoA dehydrogenase (MCAD), long-chain acyl-CoA dehydrogenase (LCAD), and very long-chain acyl-CoA dehydrogenase (VLCAD). The increased hepatic FAO increases the production of acetyl CoA, which on condensation with acetoacetyl CoA generates HMG-CoA and CoA as ketone bodies. Available evidence demonstrates that PPARα upregulates the expression of the gene fibroblast growth factor 21 (FGF-21) for upregulation of genes related to lipid and ketone metabolism in response to ketogenic diet (KD) (high fat, low carbohydrate diet)-fed obese mice. Moreover, PPARα activation markedly prevents hepatic inflammation by suppression of LPS-dependent production of inflammatory cytokines, IL-1, IL-6, and TNF-α, and adhesion molecules, ICAM-1 and VCAM-1 in the aorta. In suppression of inflammation, PPARα directly or indirectly interacts with the transcription factors to upregulate the expression of anti-inflammatory genes, interleukin-1 receptor antagonist (IL-1Ra), and IκBα, a cytoplasmic inhibitor of NF-κB, to block their activity. In addition, activated PPARα prevents hepatic fibrosis through upregulation of the expression of antioxidant enzyme, catalase (CAT), in the liver to reduce the levels of ROS-induced TGFβ and collagen production by hepatic stellate cells. The agonists of PPARα stimulate the activity of PPARα by increasing the expression of adiponectin for adiponectin-mediated activation of AMPK. Moreover, AMPK activation reduces FoxO1-dependent lipid synthesis by suppression of the expression of lipogenesis-related genes, LXRα, SREBP-1c, ACC, and FAS. AMPK on activation increases the phosphorylation of ACC to inhibit its action in the synthesis of malonyl-CoA, a potent inhibitor of CPT-1, which controls the entry of fatty acids into mitochondria for oxidation or conversion into ketone bodies in the liver. Therefore, the stimulation of lipid metabolism through AMPK-dependent PPARα activation in the liver, skeletal muscle, and WAT is a potential therapeutic approach in the treatment of obesity (Pawlak et al. 2015; Yoon 2009; Higuchi et al. 2008; Houmard 2008; Stienstra et al. 2007; Badman et al. 2007; Flier 2004). A variety of phytochemicals and extracts of plants and fungi have been reported to increase the expression levels of PPARα in the liver and skeletal muscle of obese animals for improvement of postprandial hyperlipidemia and hepatic steatosis through AMPK activation (Table 4.1).

4.5.6 Modulation of Gut Microbiota Composition

Gut microbiota (GM) present on the surface of the intestinal mucus membrane in humans plays a key role in the preservation of body homeostasis through maintenance of lipid and carbohydrate metabolism. Humans have two interacting genomes, their own and that of their host microbiome, the majority of them are colonized in the gut in the layer of mucin glycoproteins produced by a specific endothelial cells, called goblet cells (Zeng et al. 2012). The gut microbiome maintains a symbiotic relationship with the host and provides vitamins and other nutrients to the host cells and thereby establishes a beneficial ecosystem for the host's physiological functions and protects the host from the entry of harmful pathogens. Their symbiotic communication results in the accuracy of the mucosal barrier function by production of mucins and antimicrobial peptides and anti-inflammatory cytokines including IgA and IL-22 and maintenance of immune tolerance (Cani 2018; Vieira et al. 2016; Brown et al. 2013).

Several environmental factors, such as high fat and high carbohydrate diet, high dose of antibiotic intake, and excessive stress, result in the change of the relative abundance levels of different classes of health-promoting bacterial community, leading to an imbalance or dysbiosis of GM, and contribute to the progression of various diseases including gastrointestinal cancers, inflammatory bowel disease, obesity, and diabetes. Therefore, modulation of GM dysbiosis by intake of health promoting natural plant/algae/mushroom/marine animals extracts rich in antioxidant and anti-inflammatory phytochemicals including dietary fibers and proteins may be a potential therapeutic target for treatment of obesity and diabetes (Ortuno Sahagun et al. 2012; Wu et al. 2011). Various classes of phytochemicals including dietary proteins and fibers, nondigestible polysaccharides and digestible polyphenolics, carotenoids, and thiosulfides present in dietary fruits, vegetables, legumes, and beverages stimulate the growth of some beneficial bacterial species, such as bacterial spp. of genera, *Bifidobacterium*, *Lactobacillus*, yeast, *Prevotella*, and *Akkermansia*, which improve the insulin sensitivity in the metabolic tissues for metabolism of lipid and carbohydrate of the host through production of short-chain fatty acids (SCFAs) and branched-chain amino acids (BCAA) and increase innate immunity of the body for treatment of obesity and diabetes (Carrera-Quintanar et al. 2018). A good number of natural products have been reported to modulate GM dysbiosis for treatment of obesity and diabetes in animal models (see in the next section). The major therapeutic targets of natural products are presented in Fig. 4.2.

4.6 Natural Products Isolated from Various Natural Sources in Treatment of Obesity

A variety of natural products, including crude extracts of plants, mushrooms, marine algae, microorganisms, and animals and isolated phytochemicals from these extracts, have been reported to prevent obesity in cellular and animal models. Several review articles have highlighted antiobesity effects of natural products

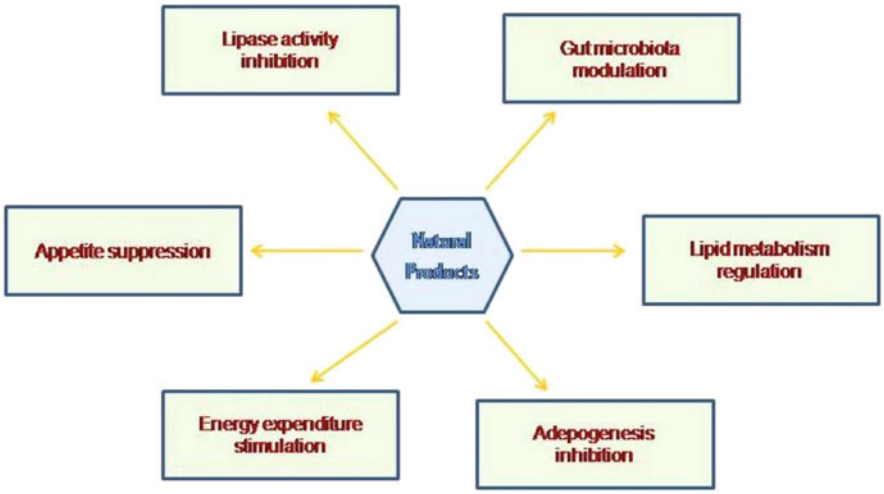

Fig. 4.2 Major therapeutic targets of natural products in obesity treatment

from diverse sources, but none of them provide the details of the mechanisms of action and active constituents of the bioactive extracts (Yun 2010; Fu et al. 2016; Mopuri and Islam 2017; Karri et al. 2019). Table 4.1 provides a comprehensive list of some natural products (extracts and bioactive components) in obesity treatment and their major modes of actions.

From the Table 4.1, it is evident that the plants from 59 families have been reported to possess antiobesity activity. Among these families, 10 families, namely, *Apiaceae*, *Araliaceae*, *Asteraceae*, *Celastraceae*, *Dioscoreaceae*, *Fabaceae, Lamiaceae*, *Solanaceae*, *Theaceae*, and *Zingiberaceae*, contribute a large number of plants and phytochemicals having antiobesity potentials. Most of the plants and their active phytochemicals reduce insulin resistance in obese animals by upregulation of lipid metabolism and energy expenditure through AMPK activation in the liver, adipose tissue, and skeletal muscle. Among the bioactive phytochemicals, flavonoids, and saponins have been shown to possess strong antiobesogenic potential for amelioration of the pathogenesis of obesity via multi-molecular targets in metabolic tissues including lipid and energy metabolism, modulation of gut dysbiosis composition, inhibition of pancreatic lipase activity, and suppression of appetite. Some edible and medicinal mushrooms including *Auricularia polytricha*, *Grifola frondosa*, *Ganoderma lucidum*, and *Pleurotus sajor-caju* have been found to have potential antiobesity effects via their polysaccharides and other phenolic and terpenoid phytochemicals. Marine algae, especially edible seaweeds, are a promising source of antiobesity agents. Four major classes of bioactive compounds, namely, carotenoids (fucoxanthin and astaxanthin), alginates (gelling-like polysaccharides), fucoidans (sulfated polysaccharides), and phlorotannins, present in these seaweeds are responsible for the antiobesity activity of these seaweeds. Usually, carotenoids and fucoidans inhibit lipid synthesis and

lipid absorption in the body, and alginates suppress appetite. Brown seaweeds, namely *Ecklonia cava*, *E. stolonifera*, *Undaria pinnatifida*, *Ishige okamurae*, and *Laminaria japonica* contain high concentrations of phlorotannins and carotenoids as bioactive components for inhibition of adipogenesis and lipogenesis and pancreatic lipase activity. Among these brown algae, *E. cava* contains the highest amounts of phlorotannins (Hu et al. 2016b). Polyunsaturated fatty acids, mainly eicosapentaenoic acid and docosahexaenoic acid isolated from Antarctic krill, have potential antioxidant, lipid catabolism, and insulin sensitivity effects. These natural products could be useful for clinical trials in humans for treatment of obesity after their extensive toxicological and pharmacokinetic studies.

4.7 Major Therapeutic Targets of Natural Products in Diabetes Treatment

4.7.1 Stimulatory Effect on AMPK Activation

In humans, the maintenance of normal glucose levels depends on the responsiveness of insulin in skeletal muscle and liver and insulin secretion from pancreatic beta cells. Both these factors are the main pathophysiological features of type 2 diabetes because of insulin resistance in the skeletal muscle and liver and impaired insulin secretion from pancreatic beta cells due to lipotoxicity and glucotoxicity in these metabolic tissues. AMP-activated protein kinase (AMPK) is a highly conserved sensor of cellular energy and its activation inhibits fat synthesis and fat accumulation by promoting lipolysis and fat oxidation and enhances mitochondrial function and biogenesis via phosphorylation of PGC-1α and induction of the expression of energy metabolism-related genes. Moreover, AMPK activation in skeletal muscle promotes glucose uptake via upregulation of GLUT4 expression and its translocation from intracellular storage vesicles to the plasma membrane for reduction of plasma glucose levels (Kelley et al. 2002; Lowell and Shulman 2005; Mcgee et al. 2008). In addition, activation of AMPK by its activator, 5-aminoimidazole-4-carboxamide riboside (AICAR), and other AMPK agonists downregulates the expression of gluconeogenic genes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) in the liver to inhibit hepatic glucose production (Lochhead et al. 2000). Furthermore, phosphorylated AMPK inactivates two key enzymes of fatty acid and sterol synthesis, acetyl-CoA carboxylase-1 (ACC1) and 3-hydroxy-3-methylglutaryl-CoA reductase HMGCR), in the liver and adipose tissue (Hardie et al. 1989). In the brain, adipokine leptin sensitivity inhibits the activation of AMPKα2 to reduce both body weight and food intake, whereas adipokine adiponectin and stomach gastric peptide ghrelin promote its activation to increase food intake and energy expenditure (Minokoshi et al. 2004). Available evidence indicates that AMPK exists as heterotrimers composed of a catalytic α-subunit and regulatory β-and γ-subunits. Its α1 isoform predominates in the liver and adipose tissue, while its α2 isoform is mainly expressed in the muscle, brain, and heart (Hardie et al. 2012). AMPK activation depends on its phosphorylation of the

catalytic subunit α on threonine 172 by liver kinase B-1 (LKB1) or calcium-dependent calcium/calmodulin-dependent protein kinase kinase beta (CaMKKβ), and this is promoted by AMP or ADP binding to the γ-unit. Therefore, an increase of cellular AMP/ATP ratio or ADP/ATP ratio promotes AMPK activation (Oakhill et al. 2011; Xiao et al. 2011).

Several phytochemicals from natural products, namely, curcumin from *Curcuma longa*, resveratrol from *Vitis vinifera*, crytotanshinone from *Salvia miltiorrhiza*, berberine from *Coptis chinensis*, ginsenosides from *Panax ginseng*, epigallocatechin gallate from green tea, theaflavin from black tea, arctigenin from *Arctium lappa*, aspalathin from *Aspalathus linearis*, sophoricoside from *Sophora japonica*, p-coumaric acid from *Ganoderma lucidum*, and cyanidin-3-*O*-β-glucoside **31** from dietary fruits (Fig. 4.1) have been shown to activate AMPK for amelioration of hyperglycemia and insulin resistance in cellular and animal models of diabetes (Table 4.2) (Hardie 2013; Huang et al. 2012; Guo et al. 2012; Son et al. 2013; Wu et al. 2013; Yoon et al. 2013).

4.7.2 Stimulatory Effect on PI3K/Akt Signaling Pathway

The insulin-regulated PI3K/Akt signaling pathway plays a central role for regulation of many cellular processes including glucose homeostasis, lipid metabolism, carbohydrate metabolism, and protein synthesis in various insulin-responsive tissues such as the skeletal muscle, liver, adipose tissue, brain, and pancreas, in the body. The defect of this signaling pathway causes abnormalities in both glucose and lipid homeostasis and ultimately leads to the development of hyperglycemia and hyperlipidemia in both obese and type 2 diabetic patients. The Akt kinase, also known as protein kinase B (PKB), is serine/threonine kinase, mainly present in three isoforms, Akt1, Akt2, and Akt3, in humans. Akt2 is mainly expressed in the insulin-responsive tissues, brown fat, skeletal muscle, and liver, while Akt1 and Akt3 are ubiquitously expressed in different tissues. About 90% of insulin-stimulated glucose utilization occurs in skeletal muscle through PI3K/Akt signaling pathway by promoting GLUT4 proteins transport from inner cell to cell surface, glycogen synthesis, and protein synthesis (Abeyrathna and Su 2015; Ueki et al. 1998).

In skeletal muscle and adipose tissue, insulin promotes the activation of its receptor, IR by phosphorylation at tyrosine residues, and phosphorylated IR increases the expression and phosphorylation of insulin receptor substrate proteins, IRS1 and IRS2, which in turn activate phosphatidylinositol-3-kinase (PI3K) by its phosphorylation. The activated PI3K stimulates the phosphorylation of intracellular Akt via successive formation of phosphatidylinositol-3,4,5-triphosphate (PIP3) and phosphoinositide-dependent kinase 1 (PDK1). The activated Akt induces phosphorylation of its substrate AS160 protein at Thr and Ser sites for expression and translocation of glucose transporter protein GLUT4 from intracellular storage vesicle to the cell surface for plasma glucose uptake in an exocytosis process stimulated by ATP signal and participation of Ras-related protein Rab 8A (Osorio-Fuentealba et al. 2013). The expression of GagPKB, an active form of PKB (Akt), increases

Table 4.2 List of some natural products (extracts/active components isolated from various natural sources) having reported antidiabetic effects and their major molecular targets and actions

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
A. Plants				
1. Achariaceae				
Hydnocarpus laurifolia	Seeds, ethyl acetate ext.	STZ-diabetic rats	Serum glucose and lipid profile↓	Sailaja Rao and Krishna Mohan (2014)
2. Acoraceae				
Acorus calamus	Rhizomes, methanol ext., ethyl acetate fr	STZ-diabetic rats, obese diabetic mice, L6 cells, enzyme inhibition assay	Plasma glucose and lipid profile↓, insulin secretion and glycogen synthesis↑, glucose uptake in L6 cells↑, plasma adiponectin, GLP-1 expression, insulin secretion, insulin action in diabetic mice↑, α-glucosidase activity↓	Prisilla et al. (2012), Si et al. (2010), Liu et al. (2015b)
3. Actinidiaceae				
Actinidia deliciosa	Fruits, methanol ext.	Alloxan-diabetic rats	Plasma glucose, TG, TC, GOT, GPT↓, insulin secretion, plasma HDL-C↑	Soren et al. (2016)
4. Aizoaceae				
Zaleya decandra	Roots, ethanol ext.	Alloxan-diabetic rats	Plasma glucose, TG, TC, urea, creatinine↓, pancreatic and liver function↑	Meenakshi et al. (2010)
5. Amaranthaceae				
Amaranthus paniculatus	Leaves, ethanol ext.	Alloxan-diabetic rats	Plasma glucose, TG, TC, CRP, GPT, GOT↓, pancreatic islet mass↑	Nawale et al. (2017)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
A. spinosus, *A. viridis*	Leaves, methanol ext.	STZ-diabetic rats	Plasma glucose, TG, TC, LDL-C↓, body weight gain, plasma HDL-C, pancreatic β-cell mass↑	Krishnamurthy et al. (2011), Girija et al. (2011)
6. Amaryllidaceae				
Allium sativum	Bulb, ethanol ext.	STZ-diabetic rats	Plasma glucose, TG, TC, urea, creatinine, AST, ALT↓, insulin secretion, lipid metabolism↑	Eidi et al. (2006)
7. Anacardiaceae				
Anacardium occidentale	Leaves, ethanol ext.	STZ-diabetic rats	Plasma glucose, TG, TC, LDL-C↓, liver and kidney function↑	Jaiswal et al. (2017)
Mangifera indica (mango)	Leaves, water ext., mangiferin **336a**	STZ-diabetic rats	Plasma glucose, TC, TG, LDL-C, AI, MDA↓, Plasma HDL-C, insulin secretion, insulin action↑	Villas Boas et al. (2020), Muruganandan et al. (2005)
Pistacia lentiscus	Leaves and fruits, ethanol ext., flavonoids and tannins	STZ-diabetic rats, enzyme inhibition assay	Plasma postprandial glucose, AST, ALT, ALP, bilirubin↓, liver and kidney function↑, α-amylase activity↓	Mehenni et al. (2016)
Rhus coriaria	Fruits, water ext.	STZ-diabetic rats, enzyme inhibition assay	Plasma glucose, HbA1c, TG, TC, LDL-C↓, plasma HDL-C, liver and kidney function↑, α-glucosidase activity↓	Dogan and Celik (2016)
R. mysorensis	Leaves and rhizomes, aqueous ethanol ext., flavonoids	Enzyme inhibition assay, STZ-diabetic rats	α-Amylase, α-glucosidase activity↓, plasma glucose↓	Rani et al. (2017)

Spondias tuberosa	Inner stem-bark, aqueous ethanol ext	STZ-diabetic rats	Plasma glucose, TC, TG, VLDL↓, insulin action, liver function, antioxidant activity↑	Barbosa et al. (2018)
8. Apiaceae				
Angelica dahurica	Roots, methanol ext., n-hexane fr, phellopterin (**337**)	GLUTag cells, INS-1 cells, diabetic db/db mice	Insulin secretion in INS-1 cells↑, GLP-1 secretion in GLUTag cells↑, plasma glucose↓, GPR119 expression in pancreatic islet and GLUTag cells↑	Park et al. (2016)
A. sinensis	Roots, water ext., polysaccharide	STZ-diabetic rats	Plasma glucose, TG, TC, TNFα, IL-6↓, Insulin action, liver and muscle glycogen content↑	Wang et al. (2015a)
Centella asiatica	Leaves, 70% ethanol ext.	Obese diabetic rats	Plasma glucose, TG, TC↓, pancreatic insulin secretion↑	Maulidiani et al. (2016)
Ferula asafoetida	Oleo-gum, ethanol ext., ferulic acid **72**	STZ-diabetic rats	Serum FG, TC, LDL-C, GOT, GPT, creatinine, urea↓, serum HDL-C, pancreatic insulin secretion↑	Latifi et al. (2019)
Pimpinella anisum	Leaves, 80% methanol ext.	Enzyme inhibition assay, diabetic patients	α-Amylase, α-glucosidase, pancreatic lipase activity↓, plasma glucose, LDL-C, VLDL-C, MDA, LPO↓, plasma HDL-C↑	Shobha and Andallu (2018)
Pimpinella brachycarpa	Leaves, 70% ethanol ext.	HF-HS-fed diabetic mice, enzyme inhibition assay	Plasma glucose, insulin, HOMA-IR, TG, TC↓, plasma adiponectin, liver SOD, CAT, GP_X↑, activity of α-glucosidase↓	Lee et al. (2013)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
9. Apocynaceae				
Acanthus montanus	Leaves, methanol ext	Enzyme inhibition assay	α-Amylase and α-glucosidase activity↓	Ogundajo et al. (2016)
Adhatoda vasica	Leaves and roots, ethanol ext., vasicine (**338**), vasicinol (**339**)	Enzyme inhibition assay	α-Amylase, α-glucosidase activity↓	Gao et al. (2008)
Andrographis paniculata	Whole plant, 90% ethanol ext., andrographolide (**335**)	L6 myotubes, HF-Fruc-fed diabetic rats	GLUT4 expression in L6 myotubes↑, plasma glucose, TG, TC↓, glucose uptake in muscle and adipose tissue↑	Nugroho et al. (2012)
Barleria prionitis	Leaves and roots, ethanol ext.	Alloxan-diabetic rats	Plasma glucose↓, pancreatic insulin secretion, glycogen synthesis, glucose uptake in liver↑	Dheer and Bhatnagar (2010)
Catharanthus roseus	Leaves, powder or ethanol ext.	STZ-diabetic rats	Glucose metabolism↑, plasma glucose, TC, TG, LDL-C, VLDL-C↓, pancreatic insulin secretion, muscle and liver glycogen content, expression of GLUT4, GLUT2, GS, GCK, GPDH↑	Singh et al. (2001), Rasineni et al. (2010), Al-Shaqha et al. (2015)
Gymnema sylvestre	Leaves, acetone ext., dihydroxy-gymnemic triacetate (**340**)	STZ-diabetic rats	Serum glucose, HbA1c, TC, TG, LDL-C, AST↓, serum HDL-C, insulin, muscle and liver glycogen content↑	Daisy et al. (2009)
Holarrhena antidysenterica	Seeds, water ext.	STZ-diabetic rats	Plasma glucose, TG, TC, LDL-C, VLDL-C, plasma, liver and kidney GOT, GPT↓, plasma HDL-C, liver and muscle glycogen content, GCK, GPDH↑	Ali et al. (2011)

10. Asteraceae				
Artemisia amygdalina	Whole plant, aqueous-ethanol	STZ-diabetic rats	Plasma glucose, TC, TG, LDL-C, creatinine, hepatic GOT, GPT, food intake↓, pancreatic β-cell mass↑	Ghazanfar et al. (2014)
A. sphaerocephala	Seeds, water ext.	STZ-diabetic rats	Plasma FG, HbA1c, TC, TG↓, Plasma HDL-C, hepatic GCK expression, glycogen content↑, hepatic fat content, insulin resistance↓	Xing et al. (2009)
Cichorium intybus	Whole plant, 80% ethanol ext.	STZ-diabetic rats	Serum glucose, TG, TC↓, hepatic G6Pase expression↓, pancreatic insulin secretion↑	Pushparaj et al. (2007)
Elephantopus scaber	Roots, water ext.	Alloxan-diabetic rats	Serum glucose, HbA1c, TG, TC, creatinine, urea↓, pancreatic β-cell mass and function, liver glycogen content↑	Daisy et al. (2007)
Stevia rebaudiana	Leaves, ethanol ext., polyphenol-rich fr	STZ-diabetic rats	Serum glucose, ALT, AST, MDA↓, Hepatic insulin action, GSH, SOD, CAT, kidney GPDH↑, urine volume↓	Shivanna et al. (2013)
Wedelia calendulacea	Whole plant, methanol ext., wedelolactone **341**	STZ-diabetic rats, enzyme inhibition assay	Serum glucose, TG, Tc, LDL-C, VLDL-C, CRP, TNFα, IL-6↓, α-amylase, α-glucosidase, DPP-4 activity↓, pancreatic β-cell regeneration and function, serum HDL-C↑	Kumar et al. (2018)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
11. Begoniaceae				
Begonia malabarica	Stems, methanol ext.	STZ-diabetic rats	Serum glucose, urea, creatinine, GPT↓, hepatic glycogen content↑, kidney weight↓	Pandikumar et al. (2009)
12. Caprifoliaceae				
Lonicera japonica	Stems, 70% ethanol ext., loganin (**342**), sweroside (**343**)	HFD-fed STZ-diabetic rats	Serum FG, HOMA-IR↓, muscle PPARγ expression, hepatic IRS-1 expression, pancreatic β-cell mass and function↑	Han et al. (2015a)
13. Cistaceae				
Cistus laurifolius	Leaves, ethanol ext., flavonoids	STZ-diabetic rats, enzyme inhibition assay	Serum glucose↓, α-amylase, α-glucosidase activity↓	Orhan et al. (2013)
C. salviifolius	Aerial parts, water ext.	Enzyme inhibition assay, STZ-NA-diabetic rats	α-Amylase, α-glucosidase activity↓, plasma glucose, TG, creatinine↓, pancreatic islet mass↑	Sayah et al. (2017, 2020)
14. Combretaceae				
Anogeissus leiocarpus	Leaves, ethanol ext.	Alloxan-diabetic rats	Serum FG, TC, TG, LDL-C↓, hepatic glycogen content↑	Onoja et al. (2018)
15. Cornaceae				
Alangium lamarckii	Leaves, ethanol ext.	STZ plus NA-diabetic rats	Plasma glucose, TG, TC, LDL-C, TRABS↓, plasma HDL-C, hepatic glycogen content, SOD, CAT activity↑	Kumar et al. (2011)

16. Cucurbitaceae				
Citrullus lanatus	Fruit-juice, flavonoids	Alloxan-diabetic rats, SD-diabetic rats, enzyme inhibition assay	Plasma FG and PPG, TC, TG, LDL-C, VLDL-C, MDA, TNFα, IL-6, ALP↓, plasma HDL-C, hepatic glycogen content, expression of hepatic GK, GLUT2, GLUT4, GSH, SOD, CAT↑, expression of hepatic G6Pase, activity of α-amylase and α-glucosidase↓	Ajiboye et al. (2020), El-Razek and Sadeck (2011)
Cucumis sativus	Fruits, ethanol ext.	STZ-diabetic rats	Plasma FG, PPG, TG, TC, LDL-C, VLDL-C↓, Plasma HDL-C, pancreatic β-cell function↑	Karthiyayini et al. (2009)
Cucurbita ficifolia	Fruits, water ext.	STZ-diabetic rats	Plasma FG, MDA, food intake↓, hepatic, kidney and pancreas GSH, GP_X, GR, GSH/GSSG ratio↑	Diaz-Flores et al. (2012)
Cucurbita pepo (pumpkin)	Fruits, powder, polysaccharides	Alloxan-diabetic rats	Serum FG, TG, TC, LDL-C, CRP↓, Serum insulin, HDL-C, hepatic glycogen, pancreatic islets mass↑	Sedigheh et al. (2011), Wang et al. (2017c)
Luffa acutangula	Fresh fruits, aqueous-methanol ext., saponins, flavonoids	STZ plus NA-diabetic rats, enzyme inhibition assay	Serum FG, HbA1c, insulin, TC, TG, LDL-C, VLDL-C, AST, ALT↓, serum HDL-C, hepatic glycogen content↑, α-glucosidase activity↓	Pimple et al. (2011)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
Momordica charantia	Green fruits, ethanol ext., ethyl acetate fr, 9c,11t,13t-conjugated linolenic acid (**343a**), seed, chloroform ext., polypeptide k	Alloxan-diabetic rats, 4H11EC3 cells, enzyme inhibition assay	Plasma glucose, HbA1c, TC, TG, LDL-C, pancreatic necrosis↓, Plasma insulin, HDL-C, total proteins, liver glycogen content↑, Expression of PPARα, ACOX in H411EC3 cells↑, Activity of α-amylase and α-glucosidase↓	Fernandes et al. (2007), Chuang et al. (2006), Ahmad et al. (2012)
Trichosanthes cucumerina	Whole plant, water ext.	STZ-diabetic rats	Serum FG↓, Liver and muscle glycogen content↑	Kirana and Srinivasan (2008)
17. Dilleniaceae				
Dillenia indica	Leaves, ethanol ext., chromane derivative (3,5,7-trihydroxy-2 (4-hydroxybenzyl)-chroman-4-one) (**344**)	STZ-diabetic rats	Serum FG, TC, TG↓, Antioxidant enzyme activity in liver↑	Kaur et al. (2016)
18. Dioscoreaceae				
Dioscorea alata	Tubers, ethanol ext., flavonoids, anthocyanins	Alloxan-diabetic rats	Serum FG, TC, TG, LDL-C, VLDL-C, creatinine↓, serum proteins, HDL-C↑	Maithili et al. (2011)
D. batatas	Tubers, 50% ethanol ext., allantoin (**345**)	STZ-diabetic rats	Plasma FG, TC, TG, LDL-C, creatinine, CK, uric acid, MDA, LDH, ALT, AST↓, plasma insulin, C-peptide, proteins, GSH, SOD, tGSH↑, pancreatic β-cell mass and function↑	Go et al. (2015)

19. Ericaceae				
Vaccinium myrtillus (bilberry)	Fruits, powder, anthocyanins	Alloxan-diabetic rats	Serum glucose, TC, TG, LDL-C, VLDL-C↓, serum HDL-C, insulin, pancreatic islet size↑	Asgary et al. (2016)
V. vitis-idaea (lingonberry)	Berries, ethanol ext.	HFD-fed obese diabetic mice	Lipid metabolism and insulin sensitivity↑, serum glucose, insulin, TC, LDL-C, muscle acetyl p53↓, muscle and liver AMPK, Akt activation, muscle GLUT4, SIRT1 expression↑	Eid et al. (2014)
20. Ebenaceae				
Diospyros melanoxylon	Leaves, pet ether ext.	STZ-diabetic rats	Serum FG, TC, TG, food intake↓, serum HDL-C↑, lipogenesis↓	Rathore et al. (2014)
21. Elaeocarpaceae				
Aristotelia chilensis (maquiberry)	Fruits, 70% methanol ext., anthocyanin-rich fr, delphinidin glucoside	HFD plus STZ-obese diabetic mice, L6 cells, H411E cells	Plasma FG, insulin↓, glucose uptake in muscle and L6 cells↑, expression of G6Pase in liver and H411E cells↓	Rojo et al. (2012)
22. Euphorbiaceae				
Croton lobatus	Leaves, methanol ext.	Alloxan-diabetic rats	Plasma glucose, TC, TG, LDL-C, VLDL-C, MDA, NO↓, hepatic and plasma SOD, GSH activity↑, pancreatic islet cells integrity↑	Fasola et al. (2016)
23. Fabaceae				
Albizia lebbeck	Barks, methanol ext.	STZ plus NA-diabetic rats	Plasma FG, TC, TG, LDL-C, VLDL-C, urea, creatinine↓, plasma HDL-C↑	Patel et al. (2015)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
Astragalus membranaceus	Roots, hot water ext., polysaccharides	HFD-fed obese diabetic mice	Hepatic fat mass and TG content, plasma FG, insulin, HOMA-IR↓, Expression of hepatic PTP1B and XBP1↓	Mao et al. (2009)
Caesalpinia bonducella syn, *C. crista*, *C. bonduc*	Seeds, aqueous and ethanol ext.	STZ-diabetic rats	Plasma FG, TC, TG↓, pancreatic insulin secretion, liver glycogen content↑	Chakrabarti et al. (2005)
C. bonduc	Leaves, ethanol ext., polyphenolic fr rich in gallic-, caffeic-, p-coumaric-, and chlorogenic acids	Alloxan-diabetic rats	Plasma glucose, HbA1c, amylin, leptin, PYY↓, expression of hepatic G6Pase, FBPase, pancreatic p-MAPK-8↓, insulin secretion and sensitivity↑, hepatic glycogen content, expression of hepatic HK, GPDH, IRS-1, GLUT4, pancreatic Ins-1, Pdx-1, hepatic and pancreatic SOD, CAT, GSH, GP_X↑	Iftikhar et al. (2020)
Desmodium gangeticum	Aerial parts, 50% aqueous-ethanol ext.	STZ-diabetic rats, MIN6 cells	Plasma glucose, TG, TC↓, Plasma HDL-C↑, insulin secretion in MIN6 cells↑	Govindarajan et al. 2007)
Medicago sativa (alfalfa)	Aerial parts, water ext.	Alloxan-diabetic rats	Plasma glucose, TC, TG, LDL-C, VLDL-C, AST↓, liver and pancreatic injury↓, Plasma HDL-C↑	Farsani et al. (2016)
Mimosa pudica	Leaves, methanol ext.	STZ-diabetic rats	Plasma glucose, TC, TG, LDL-C, VLDL-C, ALT, urea, creatinine↓, plasma HDL-C↑, pancreas, liver and kidney injury↓	Parasuraman et al. (2019)

Pterocarpus marsupium	Bark, ethanol ext., butanol fr	Alloxan-diabetic rats	Plasma glucose, TC, TG, ALP, GOT, GPT↓, plasma proteins↑	Dhanabal et al. (2006)
Trigonella foenum-graecum (methi)	Seeds, aqueous-ethanol ext., 4-hydroxyisoleucine (**345a**), trigonelline (**345b**), diosgenin (**345c**), galactomannan (**345d**)	HFD-fed diabetic C57BL/6J mice, STZ-diabetic rats	Serum glucose, insulin, TG, HOMA-IR↓, serum HDL-C, liver CAT, hepatic, pancreatic and renal functions↑	Hamza et al. (2012), Baset et al. (2020)
24. Gentianaceae				
Enicostemma littorale	Whole plant, methanol ext.	Alloxan-diabetic rats	Serum glucose, LPO, expression of hepatic G6Pase↓, serum insulin, GSH↑	Maroo et al. (2003)
25. Hypoxidaceae				
Curculigo latifolia	Fruits and roots, water ext	HFD plus STZ-obese diabetic rats	Insulin-stimulated glucose and lipid metabolism↑, plasma glucose, TC, TG, LDL-C, ALT, urea, creatinine↓, plasma HDL-C, insulin, adiponectin, expression of IRS1, GLUT4, IGF1, PPARα, PPARγ, adipoR, LPL in muscle and AT↑	Ishak et al. (2013)
26. Iridaceae				
Crocus sativus	Stigma, ethanol ext., crocin (**346**), safranal (**347**)	Alloxan-diabetic rats, type 2 diabetic patients, STZ-diabetic rats	Serum FG, TG, TC, LDL-C in both diabetic rats and diabetic patients↓, serum insulin, HDL-C, GSH, SOD, CAT, pancreatic β-cell mass and function in diabetic rats↑	Mohajeri et al. (2009), Samarghandian et al. (2017), Aleali et al. (2019)
27. Lamiaceae				
Callicarpa nudiflora	Leaves, 80% ethanol ext., iridoids, phenyl propanoids	STZ plus HFD-type 2 diabetic rats	Insulin signaling and AMPK activation↑, plasma FG, TC, TG, LDL-C, HOMA-IR↓, Plasma HDL-C, expression of p-AMPK, p-ACC, GLUT4 in muscle, IRS-1 in liver↑	Ma et al. (2014)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
Marrubium vulgare	Aerial parts, aqueous and methanol ext., verbascoside **348**, luteolin-7-*O*-glucoside **349**	STZ-diabetic rats	Glucose utilization and insulin secretion↑, serum FG, TC, TG, LDL-C, MDA↓, serum insulin, HDL-C, muscle and hepatic glycogen content, expression of hepatic antioxidant enzymes GSH, GP_X, GR, GST↑	Elberry et al. (2015), Boudjelal et al. (2012)
Ocimum sanctum	Leaves, hexane ext., fixed oil, α-linolenic acid (**350**)	STZ-diabetic rats	Renal oxidative stress↓, serum glucose, TC, TG, LDL-C, creatinine, BUN, TBARS, kidney weight↓, serum insulin, HDL-C, activity of CAT, SOD, GP_X in renal tissue↑	Suanarunsawat et al. (2016)
Origanum majoranum	Leaves, hot water ext.	STZ plus diet-type 2 diabetic rats	Glucose and lipid metabolism↑, serum glucose, TC, TG, LDL-C, VLDL-C, insulin, leptin, hepatic and kidney lipid mass↓, serum HDL-C, expression of adiponectin, PPARγ, LPL in AT, GLUT2 in liver↑	Soliman et al. (2016)
Otostegia persica	Aerial parts, hot water ext.	STZ-diabetic rats	Serum FG, TG, HOMA-IR↓, serum HDL-C, pancreatic mass and insulin secretion↑	Akbarzadeh et al. (2012)
Phlomis persica	Aerial parts, 80% methanol ext., iridoid glycosides	STZ-diabetic rats	Hepatic oxidative stress↓, serum FG, hepatic TBARS↓, serum insulin, hepatic SOD, CAT, GP_X↑	Sarkhail et al. (2010)

Salvia officinalis	Leaves, ethanol and methanol ext.	STZ-diabetic rats	Serum glucose, TG, TC, urea, uric acid, creatinine, AST, ALT↓, Serum insulin↑	Eidi and Eidi (2009), Eidi et al. (2005)
28. Lythraceae				
Punica granatum (pomegranate)	Fruits, aqueous-methanol ext., ethyl acetate fr, or aqueous ext., gallic acid, ellagic acid, valoneic acid dilactone (**350a**)	Alloxan-diabetic rats, enzyme inhibition assay	Glucose and lipid metabolism, insulin secretion and action↑, serum FG, PPG, TG, FFAs↓, serum insulin, muscle and liver glycogen content, expression of IRS1, Akt, GLUT4, GLUT2, p-Akt↑, pancreatic β-cell function and regeneration↑, activity of α-amylase and PTP1B↓	Jain et al. (2012), Gharib and Kouhsari (2019)
29. Malvaceae				
Grewia asiatica	Fruits, ethanol ext.	STZ-diabetic rats	Insulin signaling↑, serum glucose, MDA, TNFα, IL-1β↓, liver glycogen content, hepatic SOD, GSH activity, pancreatic insulin secretion↑	Khattab et al. (2015)
Helicteres isora	Roots, aqueous-ethanol ext., butanol fr	Alloxan-diabetic rats	Serum glucose, TC, TG, urea↓, pancreas, liver, and kidney function↑	Venkatesh et al. (2010)
Hibiscus rosa-sinensis	Leaves, ethanol ext., chloroform fr	Non-obese diabetic mice	Serum glucose, HbA1c, TC, LDL-C, VLDL-C, urea↓, serum HDL-C, insulin↑	Moqbel et al. (2011)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
30. Menispermaceae				
Coscinium fenestratum	Stem, ethanol ext., berberine (**48**)	STZ plus NA-diabetic rats	Glucose utilization↑, glucose production↓, serum glucose, HbA1c, TG, TC, MDA, ALT, creatinine↓, Serum insulin, HDL-C, hepatic glycogen content, expression of hepatic HK, GPDH, CAT, SOD, GSH, GP_X↑, expression of G6Pase in liver and kidney↓	Shirwaikar et al. (2005), Punitha et al. (2005)
Tinospora cordifolia	Roots and stems, 70% ethanol, aqueous methanol ext., palmatine (**130**)	Alloxan-diabetic rats and STZ-diabetic rats, L6 myotubes	Carbohydrate metabolism and antioxidant status↑, serum glucose, HbA1c, ALP, LDH, MDA↓, serum insulin, C-peptide, expression of hepatic HK, PPARα, SOD, GSH, GP_X, hepatic and muscle glycogen content, pancreatic insulin secretion↑, expression of hepatic and kidney G6Pase, FBPase↓, expression of GLUT4 in L6 cells↑	Stanely et al. (2000), Rajalakshmi et al. (2009), Sangeetha et al. (2011, 2013)
31. Moraceae				
Ficus carica	Leaves, ethyl acetate ext., ficusin (**351**)	STZ-diabetic rats	Glucose utilization↑, serum FG, TC, TG↓, hepatic glycogen content, HK expression, pancreatic insulin secretion and β-cell regeneration↑, expression of hepatic G6Pase, FBPase↓	Irudayaraj et al. (2017)

F. lutea	Leaves, acetone ext., ethyl acetate fr	In vitro enzyme inhibition assay, cell line culture, high-calorie diet fed obese mice	Activity of α-amylase and α-glucosidase↓, insulin secretion in RIN-m5F cells↑, glucose uptake in C2C12 myotubes and H411E liver cells↑, plasma PPG↓	Olaokun et al. (2016)
F. racemosa	Stem-bark, ethanol ext., flavonoids fr rich in kaempferol (**66**), quercetin (**23**), baicalein (**352**)	Alloxan-diabetic rats and STZ-diabetic rats	Glucose metabolism and antioxidant status in liver and pancreas↑, serum FG, PLs, TC, TG, FFAs, LDL-C, VLDL-C, MDA, liver TG and TC content↓, hepatic glycogen content, body weight gain, activity of GSH, CAT, SOD in pancreas and liver↑	Sophia and Manoharan (2007), Keshari et al. (2016)
32. Musaceae				
Musa paradisiaca	Leaves and fruit peel, 70% ethanol ext.	STZ plus NA-diabetic rats	Insulin signaling↑, serum glucose, HOMA-IR, FFAs, TNFα, IL-6↓, serum insulin, C-proteins, QUICKI↑, expression of adiponectin, PPARγ, GLUT4, IRβ in AT↑	Aziz et al. (2020)
33. Myrtaceae				
Eugenia jambolana (Indian blackberry)	Fruit-pulp and seeds, ethanol, aqueous-methanol, ethyl acetate fr, gallic acid, unidentified sterol	Alloxan-diabetic rabbits, STZ-diabetic rats	Carbohydrate metabolism and pancreatic insulin secretion↑, serum FG, TC, TG, LDL-C, GOT, GPT↓, serum HDL-C, activity of SOD, CAT, GSH, GP_X in liver↑, glycogen content and expression of HK, GPDH in liver and muscle, pancreatic β-cell mass↑, expression of G6Pase, FBPase in liver↓	Mahajan et al. (2018), Chatterjee et al. (2012), Sharma et al. (2006, 2011)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
Eucalyptus tereticornis	Leaves, ethyl acetate ext., triterpenes-rich fr	STZ plus diet-diabetic rats, C2C12 cells	Carbohydrate metabolism and insulin action↑, serum FG, hepatic MCP-1, TNFα, IL-6↓, hepatic G6Pase expression↓ Glucose uptake in muscle and C2C12 cells↑	Guillen et al. (2015)
Myrtus communis	Fruits, 70% ethanol ext.	STZ-type 1 diabetic rats	Diabetic renoprotective effect↑, Serum glucose, TC, TG, BUN, MDA↓, urinary proteins excretion, urine volume↓	Talebianpoor et al. (2019)
Psidium guajava	Leaves, water ext.	STZ-diabetic rats	AMPK activation and insulin signaling↑, serum glucose, TG, TC, PLs, FFAs, LDL-C, AST, ALT↓, serum HDL-C, insulin, hepatic glycogen content, expression of IRS-1, p-Akt, p-AMPK, p-ACC, GLUT2↑, expression of G6Pase, FBPase in liver↓	Vinayagam et al. (2018)
34. Oleaceae				
Forsythia suspense	Fruits, methanol ext., ethyl acetate fr	STZ-diabetic mice, enzyme inhibition assay	Hepatic glucose metabolism and pancreatic insulin secretion↑, serum glucose, TG, TC, ACP, ALP, AST, creatinine↓, activity of α-amylase, HMGCR↓, expression of SOD, CAT, GP_X in liver and pancreas, PDX-1, INS-1, INS-2 in pancreas, GCK in liver↑, expression of G6Pase, PEPCK in liver↓	Zhang et al. (2016)

Olea europaea	Leaves, aqueous ethanol or hot water ext., oleuropein (**353**), hydroxytyrosol (**354**)	STZ-diabetic rats	Glucose metabolism and insulin signaling in liver↑, serum glucose, TC, TG, LDL-C, urea, uric acid, creatinine, CK, MDA, AST, ALT↓, serum HDL-C, insulin, hepatic glycogen content, SOD, CAT, GSH, IRS1, IRα↑	Eidi et al. (2009), Jemai et al. (2009), Al-Attar and Alsalmi (2019)
35. Orchidaceae				
Dendrobium loddigesii	Stems, aqueous-acetone ext., polyphenols-rich fr, moscatilin (**355**), gigantol (**356**)	Diabetic db/db mice	Gut microbiota dysbiosis↓, plasma glucose, LDL-C, Hepatic fat mass, TNFα↓, activity of SOD, CAT, GSH in liver, relative abundance of gut *Prevotella* and *Akkermansia*↑, relative abundance of gut *Escherichia coli* and *Rikenella* sp↓	Li et al. (2018a)
D. officinale	Roots, water ext., polysaccharides fr	STZ-diabetic rats, HepG2 cells	Insulin signaling and glucose utilization↑, serum FG, TG, TC, hepatic TG and fat content, PPARγ expression↓, activity of hepatic PEPCK, PTP1B, JNK↓, hepatic and muscle glycogen content, expression of HK, p-Akt, GLUT4↑, expression of p-IRβ, p-Akt in HepG2 cells↑	Wang et al. (2018)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
36. Oxalidaceae				
Averrhoa bilimbi	Fruits, ethyl acetate fr, quercetin	STZ-diabetic rats	Glucose metabolism↑, plasma FG, HbA1c, MDA↓, plasma insulin, hepatic antioxidant activity via CAT, GSH, GSR, GP_X↑, expression of hepatic glycolytic genes HK, PK↑, expression of hepatic gluconeogenic genes G6Pase, FBPase↓	Kurup and Mini (2017a, 2017b)
A. carambola	Fruits-juice	STZ-diabetic rats	Diabetic kidney injury↓, serum FG, TG, TC, BUN, creatinine, cAMP, MDA↓, serum insulin, SOD, sorbitol dehydrogenase↑, expression of TGFβ1, CTGF in kidney↓, pancreatic necrosis↓	Pham et al. (2017)
Biophytum sensitivum	Leaves, water ext., cupressuflavone (**357**), amentoflavone (**358**), isoorientin **302**	STZ plus NA-diabetic rats	Glucose metabolism↑, plasma glucose, HbA1c↓, plasma insulin, pancreatic insulin release, hepatic glycogen content, HK expression↑, expression of hepatic G6Pase, FBPase↓	Ananda et al. (2012)

37. Pandanaceae				
Pandanus tectorius	Fruits, ethanol ext., butanol fr rich in caffeoyl quinic acids	Diabetic db/db mice	Adiponectin-dependent AMPK activation and lipid and glucose metabolism ↑, serum FG, TG, TC, FFAs, insulin, HOMA-IR, LDL-C, leptin, TNFα, IL-6, MCP-1↓, serum adiponectin, expression of muscle GLUT4, p-AMPK, p-AS160, hepatic glycogen content, expression of HK, PPARα, CPT-1↑, hepatic fat content, expression of hepatic G6Pase, PEPCK, C/EBPα, FAS, ACC1↓	Wu et al. (2014a)
38. Phyllanthaceae				
Phyllanthus amarus	Whole plant and leaves, water ext.	STZ-diabetic rats and High-sucrose-fed diabetic rats	Oxidative stress↓, plasma FG, TG, TC, LDL-C↓, plasma HDL-C, expression of kidney CAT, SOD, GST, GR, GP_X, GSH↑	Karuna et al. (2011), Adeneye (2012)
P. niruri	Aerial parts, methanol ext., phyllanthin (**359**)	Alloxan-diabetic rats, HFD-fed obese mice, enzyme inhibition assay	Serum FG, PPG, HbA1c↓, hepatic glycogen content, expression of IRS-1/2, GLUT4, ACOX1, HSL, perilipin in liver and AT↑, expression of inflammatory genes TNFα, IL-6, NFκB, F4/80, lipogenesis-related genes PPARγ, C/EBPα, FAS, ACC in liver and AT↓, activity of α-amylase and α-glucosidase↓	Okoli et al. (2011), Jagtap et al. (2016)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
39. Plantaginaceae				
Plantago asiatica	Seeds, water ext., geniposidic acid (**360**), acteoside (**118**), isoacteoside (**361**), plantagoguanidinic acid (**362**), polysaccharides	HFD-fed obese mice, STZ plus HFD-fed diabetic rats	PPARs-dependent glucose and lipid metabolism↑, improvement of gut dysbiosis↑, serum FG, TG, TC, FFAs, MDA↓, serum HDL-C, antioxidant enzyme activity↑, hepatic fat mass and TG content, expression of aP2 in the liver↓, expression of PPARα, PPARγ, LPL, CD36, ACOX1 in liver, PGC-1α, GLUT4, Acacα in WAT, UCP1, UCP3, UCP2 in BAT of obese mice↑, relative abundance of SCFA-producing *Bacteroides vulgates*, *Lactobacillus fermentum*, *Prevotella loescheii* in gut of diabetic rats↑, rel. abundance of *Clostridium* sp., *Alistipes* sp. in gut↓	Yang et al. (2017a), Nie et al. (2019)

40. Ranunculaceae				
Nigella sativa	Seeds, ethanol ext., seed oil, thymoquinone (**363**)	STZ-diabetic rats, STZ plus HFD-fed diabetic rats, C2C12 cells, H411E cells	Glucose and lipid metabolism via insulin and AMPK activation↑, pancreatic insulin secretion↑, intestinal glucose absorption↓, plasma glucose, HOMA-IR, TG, TC, LDL-C, MDA, TNFα, NO↓, Plasma insulin, HDL-C↑, liver and muscle IRβ, PI3K, p-Akt, p-AMPK, muscle GLUT4↑, activity of SOD, CAT, GSH, GP_X in liver and kidney, SOD in pancreas↑, hepatic TIMP3↑, glucose uptake and Akt activation in C2C12 cells, H411E cells↑	Kaleem et al. (2006), Meddah et al. (2009), Abdelmeguid et al. (2010), Benhaddou-Andaloussi et al. (2011), Ali et al. (2008), Balbaa et al. (2016)
41. Rhamnaceae				
Ziziphus vulgaris syn, *Z. jujube*	Fruits, powder, kaempferol	STZ-diabetic rats, diabetic patients	Serum glucose, TC, TG, LDL-C, MDA, CRP↓, s erum insulin, HDL-C, antioxidant activity↑	Goli-malekadi et al. (2014), Yazdanpanah et al. (2017)
42. Rhizophoraceae				
Ceriops decandra	Leaves, ethanol ext.	Alloxan-diabetic rats	Glucose utilization↑, glucose production↓, plasma glucose, HbA1c↓, plasma insulin, liver glycogen content, expression of hepatic and renal HK↑, expression of hepatic and renal G6Pase, FBPase↓	Nabeel et al. (2010)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
Rhizophora mangle	Bark, acetone ext., catechins	STZ plus HFD-fed obese diabetic mice, enzyme inhibition assay	Serum FG, TC, LDL-C, insulin, leptin↓, hepatic TG content, expression of CD36, PPARγ, FAS in liver↓, activity of α-amylase, pancreatic lipase↓	Mesquita et al. (2018)
43. Rosaceae				
Amygdalus lycioides	Aerial parts, 50% ethanol ext., flavonoids	STZ-diabetic rats	Serum FG, TC, TG, LDL-C, ALP, creatinine↓, pancreatic β-cell mass and function↑	Moezi et al. (2018)
Eriobotrya japonica	Leaves and seeds, ethanol and hot water ext., flavonoids and triterpenoids including amygdalin (**364**), corosolic acid (**206**), euscaphic acid (**365**), cinchonain 1b (**366**), ursolic acid (**52**)	Alloxan-diabetic rats, HFD-fed obese mice, diabetic KK-Ay mice, INS-1 cells, enzyme inhibition assay	Insulin secretion, antioxidant activity, glucose and lipid metabolism↑, serum glucose, TG, TC↓, serum SOD, insulin↑, expression of leptin in WAT, SREBP-1c in liver↓, expression of PPARα, PPARγ in liver of obese mice↑, insulin secretion in pancreas and INS-1 cells↑, activity of 11β-HSD1↓	Tanaka et al. (2008), Chen et al. (2008), Qa'dan et al. (2009), Lu et al. (2009), Rollinger et al. (2010)
Prunus divaricata	Fruit-juice	STZ-diabetic rats	Serum FG, TC, TG, LDL-C↓, serum HDL-C↑	Minaiyan et al. (2014)
P. mume	Leaves, 70% ethanol ext., n-butanol fr, polyphenols including flavonoids	STZ plus HFD-fed diabetic rats, enzyme inhibition assay	Plasma glucose, TG↓, plasma adiponectin↑, activity of α-glucosidase↓, activity of PPARγ in AT↑	Lee et al. (2016)

44. Rubiaceae				
Paederia foetida	Leaves, methanol ext.	Alloxan-diabetic rats	Renal injury↓, plasma glucose, TG, TC, MDA, creatinine, BUN, bilirubin, AST, ALT, TNFα, IL-6↓, plasma SOD, CAT, GSH, proteins↑, expression of renal NFκBp-65↓	Borgohain et al. (2017)
45. Rutaceae				
Aegle marmelos	Fruits, water ext., eugenol (**366**), quercetin (**23**), rutin (**54**)	STZ-diabetic rats	Plasma FG, TC, TG, LDL-C, AGEs, HbA1c↓, plasma insulin, HDL-C, pancreatic mass and insulin secretion↑	Kamalakkannan and Prince (2005), Hafizur et al. (2017)
Murraya koenigii	Leaves, 70% ethanol ext., alkaloids	Enzyme inhibition assay, cell line culture	Activity of α-amylase and α-glucosidase↓, glucose uptake in L6 myotubes↑, lipid accumulation in 3T3-L1 cells↓	Parameswari et al. (2018)
Zanthoxylum aromatum	Bark, aqueous methanol ext.	STZ-diabetic rats	Serum glucose, TC, TG, LDL-C, VLDL-C, LPO↓, serum HDL-C, activity of CAT, SOD, GSH in the liver and kidney↑	Karki et al. (2014)
46. Sapotaceae				
Mimusops elengi	Leaves, ethanol ext.	STZ-diabetic rats	Serum glucose, HbA1c, TC, TG, LDL-C, PLs↓, serum insulin, HDL-C, TP, albumin, hepatic glycogen content, expression of HK, GPDH↑, expression of hepatic and renal G6Pase, FBPase↓	Jaffar et al. (2011)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
47. Solanaceae				
Lycium barbarum	Fruits, water ext., polysaccharides fr	STZ-diabetic rats	Serum glucose, insulin, leptin, AT fat mass↓, expression of melatonin and its receptor MT2 in AT↑, expression of pancreatic CLOCK, BMALI, islet growth↑	Zhao et al. (2016)
48. Urticaceae				
Urtica dioica	Leaves and aerial parts, water and 80% ethanol ext., cyclic peptide	Alloxan-diabetic rats, HFD-fed obese mice, cell line culture	Plasma FG, insulin, HOMA-IR↓, pancreatic insulin secretion, glucose uptake in muscle and C2C12 cells↑, muscle PP2A activity↓	Farzami et al. (2003), Domola et al. (2010), Obanda et al. (2016)
B. Seaweeds (Family, species)				
1. Ishigeaceae				
Ishige okamurae	50% Ethanol ext., fucoxanthin, diphlorethohydroxy-carmalol (**162**)	Diabetic db/db mice, enzyme inhibition assay	Carbohydrate metabolism↑, hepatic glucose production↓, plasma glucose, HbA1c↓, hepatic glycogen content, expression of GCK↑, expression of hepatic G6Pase, PEPCK↓, inhibited the activity of α-amylase and α-glucosidase by **162** with IC_{50} of 0.53 and 0.16 mM, respectively	Min et al. (2011), Heo et al. (2009)

2. Laminariaceae				
Laminaria japonica	Water ext., ethyl acetate fr, butyl-isobutyl-phthalate (**367**)	STZ-diabetic mice, enzyme inhibition assay	Plasma glucose↓, activity of α-glucosidase inhibited by **367** with IC_{50} of 38 μM	Bu et al. (2010)
3. Fucaceae				
Ascophyllum nodosum	Water ext., polysaccharide-rich fr, polyphenol-rich fr	STZ-diabetic mice	Plasma glucose, HbA1c, TC, TG↓, liver glycogen content, serum antioxidant activity↑, activity of α-glucosidase↓	Zhang et al. (2007)
4. Lessoniaceae				
Ecklonia cava	Water and methanol exts, dieckol-rich fr, dieckol **163**	Diabetic db/db mice, STZ-diabetic mice, enzyme inhibition assay	Plasma glucose, HbA1c, TG, TC, LDL-C, HOMA-IR↓, plasma insulin, HDL-C, hepatic glycogen content, expression of hepatic GCK, p-AMPK, p-Akt↑, plasma and hepatic SOD and CAT activity, pancreatic insulin secretion↑, expression of hepatic G6Pase, PEPCK↓, inhibited the activity of α-amylase and α-glucosidase by **163**	Lee et al. (2010a, 2012b), Kim and Kim (2012), Kang et al. (2010a)
5. Sargassaceae				
Sargassum patens	Ethanol ext., 2-(4-(3,5-dihydroxy-phenoxy)-3,5-dihydroxyphenoxy)-benzene-1,3,5-triol (**368**)	Enzyme inhibition assay	Inhibited the activity of human salivary and pancreatic α-amylase by 368 with IC_{50} of 3.2 μg/ml	Kawamura-Konishi et al. (2012)
S. ringgoldianum	80% methanol ext.	STZ-diabetic rats, enzyme inhibition assay	Plasma PPG↓, inhibited α-amylase and α-glucosidase activity with IC_{50} of 0.18 and 0.12 mg/ml, respectively	Lee and Han (2012)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
C. Macrofungi (mushrooms)				
1. Agaricaceae				
Agaricus bisporus	Mycelium powder or ethanol ext., lectin-like fiber rich in polysaccharides	STZ-diabetic rats and hypercholesterolemic rats	Glucose and lipid metabolism, insulin secretion↑, serum glucose, TG, AST, ALT, hepatic TG, TC in diabetic rats↓, serum HDL-C↑, Serum TC, TG, LDL-C in hypercholesterolemic rats↓	Jeong et al. (2010)
2. Cordycipitaceae				
Cordyceps militaris	Water ext. or acidic water ext., polysaccharides, cordycepin (**369**)	STZ-diabetic rats and mice, alloxan-diabetic rats	Glucose and lipid metabolism, antioxidant activity↑, plasma FG, TG, TC, BUN, creatinine, uric acid, urinary proteins excretion↓, plasma, pancreatic, renal and hepatic SOD, CAT, GP_X, hepatic glycogen content↑	Dong et al. 2014), Ma et al. (2015c), Zhao et al. (2018b)
3. Ganodermataceae				
Ganoderma atrum	Water ext., polysaccharide	HFD plus STZ-diabetic rats	Glucose and lipid metabolism↑, serum FG, insulin, TC, TG, LDL-C, FFAs↓, serum HDL-C, hepatic glycogen content, expression of hepatic PPARγ, GLUT4, PI3K, p-Akt, SCFAs, pancreatic Bcl-2, aortic NO, eNOS↑, pancreatic injury, Bax↓	Zhu et al. (2013, 2014, 2016)

4. Hericiaceae				
Hericium erinaceus (edible)	Water ext., polysaccharides	STZ-diabetic rats	Oxidative stress↓, glucose and lipid metabolism↑, serum glucose, TG, TC, LDL-C, MDA↓, serum insulin, HDL-C↑, serum and hepatic GSH, GP_X, SOD, CAT, activation of hepatic PI3K/Akt signaling↑	Liang et al. (2013), Cai et al. (2020)
5. Hymenochaetaceae				
Inonotus obliquus	Water ext., polysaccharides, ethyl acetate fr rich in triterpenoids and steroids	STZ-diabetic rats, alloxan-diabetic mice	Carbohydrate metabolism and antioxidant activity↑, plasma glucose, TG, TC, HbA1c, GSK-3↓, plasma insulin, HDL-C, PK, MMP-9, SOD, CAT, GP_X↑, hepatic and muscle glycogen content↑, kidney NF-κB expression↓, activity of α-amylase↓	Wang et al. (2017d), Lu et al. (2010)
Phellinus linteus	Hot water ext., polysaccharides	STZ-diabetic rats, alloxan-diabetic mice	Hepatic glucose and lipid metabolism↑, body weight gain, food intake, plasma glucose, insulin, HOMA-IR, TG, TC, LDL-C, FFAs, BUN, creatinine, uric acid, bilirubin↓, hepatic glycogen content, expression of GCK, GLUT2, LDLR, CPT1α, ACOX1↑, expression of hepatic HMGCR, FBPase, G6Pase↓	Liu et al. (2019), Zhao et al. (2014)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
6. Meripilaceae				
Grifola frondosa	Water ext., polysaccharides, ergosterol peroxide **370**	STZ-diabetic mice, KK-Ay diabetic mice, C2C12 cells	Hepatic glucose metabolism and antioxidant activity↑, gut microbiota dysbiosis↓, serum glucose, HbA1c, TG, TC, FFAs, MDA↓, Hepatic JNK1/2 activity↓, hepatic glycogen content, expression of IRS-1, PI3K, p-Akt, GLUT4, SOD, GSH, GP_X↑, rel. abundance of gut *Roseburia*, *Akkermansia*, *Lactobacillus*, *Bacteroides* spp.↑, expression of IRS-1, p-Akt, GLUT4 in high palmitate exposed C2C12 cells↑	Chen et al. (2019b), Wu et al. (2020a), Hong et al. (2007)
7. Pleurotaceae				
Pleurotus pulmonarius (edible)	Hot water ext., proteins and polysaccharides	STZ plus NA-diabetic mice, enzyme inhibition assay	Oxidative stress and dietary carbohydrate absorption↓, serum FG, PPG, TC, TG, LDL-C, VLDL-C, creatinine, BUN, MDA, LPO↓, serum HDL-C, insulin, CAT, GSSH↑, liver, kidney and pancreas necrosis↓, activity of α-amylase and α-glucosidase↓	Balaji et al. (2020), Waheb et al. (2014)

P. florida	Water ext., polysaccharides fr	STZ-diabetic rats	Oxidative stress↓, serum glucose, HbA1c, TC, TG, MDA, NO↓, excretion of urinary glucose, ketone bodies↓, serum SOD, CAT, GSH↑	Ganeshpurkar et al. (2014)
P. eryngii (edible)	Hot water ext., polysaccharides	KK-Ay diabetic mice, insulin resistant diabetic db/db mice	Glucose and lipid metabolism↑, serum glucose, HbA1c, HOMA-IR, TC, TG, LDL-C↓, serum HDL-C, liver glycogen↑	Chen et al. (2016b), Kim et al. (2010)
P. ostreatus (edible)	Methanol ext., ergosterol	KK-Ay diabetic mice, L6 myotubes	Serum FG↓, expression of p-Akt, p-PKC, GLUT4 in muscle and liver↑, expression and phosphorylation levels of AMPK, Akt, PKC, expression of GLUT4 in L6 cells↑	Xiong et al. (2018)
8. Tricholomataceae				
Catathelasma ventricosum	Water ext., polysaccharides fr (composed of mainly α-D-glucopyranose)	STZ-diabetic mice	Antioxidant activity↑, plasma glucose, TC, TG, LDL-C, MDA↓, plasma HDL-C, plasma, liver and kidney SOD, CAT, GP_X, vit C and E↑	Liu et al. (2013a)
D. Marine animals (class and species)				
1. Holothuroidea				
Cucumaria frondosa (edible sea cucumber)	Alkaline hydrolysis of freeze-dried body wall, fucoidan (polysaccharide), eicosapentaenoic acid-rich phosphatidylcholine	HF-HS-fed insulin resistant diabetic mice, STZ-diabetic rats	Serum glucose, resistin, leptin↓, serum adiponectin, hepatic glycogen↑, expression and p-levels of PI3K and Akt in muscle and AT↑, pancreatic apoptosis, expression of caspase-9 and -3↓, expression of pancreatic Bcl-xL, Bcl-2↑	Wang et al. (2016b), Hu et al. (2014, 2016a)

(continued)

Table 4.2 (continued)

(family, species)	Active plant part and fraction, active phytochemical (s)	Model	Major molecular targets and actions	References
Holothuria nobilis (sea cucumber)	Hydrolysates of water ext. with papain and protamix, peptides	STZ plus HFD-fed diabetic rats	Glucose and lipid metabolism, and insulin signaling↑, serum FG, insulin, HOMA-IR, TG, TC, LDL-C↓, expression of p-IRS1, PI3K, p-Akt in muscle 7 liver, GLUT4 in muscle, GLUT2 in liver, glycogen content in liver↑, activity of GSK-3β in liver↓	Wang et al. (2020a)
Callyspongia truncata (sponge)	Callyspongynic acid (**370a**)	Enzyme assay	α-Glucosidase activity↓	Nakao et al. (2002)
Ircinia dendroides and *I variabilis* (sponges)	Palinurin (sesquiterpene) (**370b**)	In vitro assay	GSK-3β activity↓	Bidon-Chanal et al. (2013)

glycogen synthesis in skeletal muscle L6 myotubes by increasing the activity of glycogen synthase (GS) and inhibiting the activity of glycogen synthase kinase 3β (GSK3β) via its phosphorylation in an independent of p-GSK3β pathway. This GagPKB also promotes protein synthesis in 3T3-L1 cells and L6 myotubes via phosphorylation of its substrate 4E-BP1 and p70S6K (Ueki et al. 1998; Wan et al. 2013). Moreover, Akt activation promotes the phosphorylation of forkhead O1 (FoxO1) protein for its exclusion from nucleus of hepatocytes for suppression of its activity on the expression of gluconeogenic enzymes G6Pase and PEPCK in the liver for inhibition of endogenous glucose production (Lin and Accili 2011). Akt activation in adipose tissue promotes fatty acid synthesis and cholesterol synthesis by upregulation of the expression of SREBP-1c and its target genes and inhibits lipolysis by suppression of the activity of ATGL (Chakrabarti and Kandror 2009). In pancreatic islets, PI3K/Akt signaling activation improves pancreatic β-cell mass, proliferation, and cell size and promotes insulin secretion (Bernal-Mizrachi et al. 2001).

Various phytochemicals and herbal extracts, such as 3β-taraxerol from *Mangifera indica*, catalpol and 7-hydroxyeucommiol from *Kigelia pinnata*, kaempferitrin from *Justicia spicigera*, puerarin from *Pueraria lobata*, alizarin from *Rubia cordifolia*, cyanidin-3-rutinoside **171** from *Morus nigra*, and polysaccharide from *Astragalus membranaceus*, exhibit insulin-like activity for activation of PI3K/Akt signaling pathway for improvement of hyperglycemia and hyperlipidemia in cellular and diabetic animal models (Table 4.2) (Sangeetha et al. 2010; Khan et al. 2012; Cazarolli et al. 2013; Li et al. 2014b; Xu et al. 2019; Choi et al. 2017; Liu et al. 2010a).

4.7.3 Inhibition of α-Amylase and α-Glucosidase Activity

Hydrolysis products of dietary carbohydrates (mainly starch and other related polysaccharides) are the major source of glucose in blood and main cause of postprandial high glucose levels in diabetic patients. Hydrolysis of dietary carbohydrates is carried out by a group of hydrolytic enzymes including pancreatic α-amylase and intestinal α-glucosidases. Pancreatic α-amylase hydrolyses starch into smaller oligosaccharides and disaccharides via cleavage of α-1,4-glycosidic bonds, and intestinal α-glucosidase hydrolyses these oligosaccharides and disaccharides into glucose and other monosaccharides. Therefore, the inhibition of the activity of these enzymes might be an important strategy for management of hyperglycemia in diabetic patients, wherein α-glucosidase inhibitors reduce the rapid utilization of dietary carbohydrates more effectively and thereby suppress the elevated glucose levels in postprandial hyperglycemia (Watanabe et al. 1997; Tundis et al. 2010). Currently used antihyperglycemic drugs, such as acarbose, voglibose, and miglitol, have been shown to reduce intestinal absorption of dietary sugars (Cheng and Fantus 2005). The main drawbacks of these currently used α-amylase and α-glucosidase inhibitors are their significant adverse side effects including bloating, abdominal discomfort, flatulence, and diarrhea (Derosa and Maffioli

2012; Aoki et al. 2010; Fujisawa et al. 2005). Possibly, such adverse effects might be caused by the excessive inhibition of pancreatic α-amylase activity resulting in abnormal bacterial fermentation of undigested carbohydrate diet in the colon. Some natural extracts from edible plants, seaweeds, and mushrooms and their active phytochemicals have been shown to have lower inhibitory effect against α-amylase activity and stronger α-glucosidase inhibitory activity and are therefore could be potentially effective for treatment of postprandial hyperglycemia in diabetic patients with minimal side effects (Tundis et al. 2010). For instance, proteins from bitter gourd fruit-pulp (*Momordica charantia* var. *charantia*, *M. charantia* var. *muricata*) inhibited the activity of α-amylase and α-glucosidase with IC_{50} of 0.267, 0.261, and 0.298, 0.292 mg/ml, respectively (Poovitha and Parani 2016). 6-Gingerol and oleanolic acid from *Aframomum melegueta* fruits inhibited the activity of α-amylase with IC_{50} of 81.78 and 91.72 μM and of α-glucosidase with IC_{50} of 21.55 and 17.35 μM, respectively (Mohammed et al. 2017). A 50% ethanol extract of *Orthosiphon stamineus* leaves and its active flavonoid sinensetin inhibited α-amylase and α-glucosidase activity of IC_{50} of 36.70, 1.13 mg/ml and 4.63, 0.66 mg/ml, respectively (Mohamed et al. 2012). An aqueous leaf extract of *Ocimum basilicum* (basil, tulsi) inhibited the activity of rat intestinal maltase and sucrase and porcine pancreatic α-amylase with IC_{50} of 21.31, 36.72, and 42.50 mg/mL, respectively (El-Beshbishy and Bahashwan 2012). Gamma-aminobutyric acid and ferulic acid, isolated from *Triticum aestivum* sprouts, inhibited the activity of α-amylase with IC_{50} of 5.4 and 9.5 mM/L and of α-glucosidase with IC_{50} of 1.4 and 4.9 mM/L, respectively (Jeong et al. 2012). Grape seed (*Vitis vinifera*) extract, green tea (*Camelia sinensis*) water extract and its active catechins, EGCG, GCG, and ECG, strongly inhibited the activity of α-amylase with IC_{50} of 8.7, 34.9, 24, 17, and 27 μg/ml, and of α-glucosidase with IC_{50} of 1.2, 0.5, 0.3,1.4, and 3.5 μg/ml, respectively (Yilmazer-Musa et al. 2012). Borapetoside C (**172**) from *Tinospora crispa* aqueous extract inhibited the activity of α-amylase and α-glucosidase with IC_{50} of 0.775 and 0.527 mg/ml, respectively (Hamid et al. 2015). Quercetin (**23**), found in various dietary fruits and vegetables and isolated from ethanol extract of *Callistephus chinensis*, showed strong α-glucosidase inhibitory activity with IC_{50} value of 2.04 μg/mL, similar to that of acarbose (IC_{50} of 2.24 μg/mL) (Zhang et al. 2013). A sulfated polysaccharide fucoidan from aqueous extract of marine brown alga *Ascophyllum nodosum* inhibited the activity of α-amylase and α-glucosidase with IC_{50} of 4.64 and 0.05 mg/ml, respectively (Kim et al. 2014). Moreover, a good number of extracts from plants, vegetables, seaweeds, and mushrooms and their active components having strong inhibitory effect against α-glucosidases enzymes are listed in Table 4.2.

4.7.4 Inhibition of SGLT2 Activity

Reabsorption of glucose in the kidney of humans is largely controlled by the membrane protein, sodium-glucose transporter protein 2, also known as sodium-glucose-co-transporter-2 (SGLT2). SGLT2 is expressed in high concentrations in the

proximal tubule of the kidney and is involved in glucose reabsorption and accounts for more than 90% of renal glucose reabsorption in normoglycemic conditions via an active transport of glucose through the Na^+ pump. Another SGLT enzyme, SGLT1, primarily localized in small intestine, has high affinity and low capacity for glucose reabsorption (Wright et al. 2011). Therefore, inhibition of SGLT2 activity by SGLT2 inhibitors increases urinary glucose excretion and lowers plasma glucose levels in type 2 diabetic patients in a non-insulin-dependent approach. SGLT2 inhibitors are highly effective for treatment of type 2 diabetic patients, who are failing to monotherapy and are not willing to take insulin therapy. Phlorizin (**173**) (Fig. 4.1), a dihydrochalcone glucoside, isolated from the bark of apple tree, *Malus pumila*, has been found to inhibit of human SGLT2 and SGLT1 enzyme activities with inhibitory constant Ki values of 18.6 and 151.0 nM, respectively. However, it was considered inappropriate for treatment of human diabetes because of its low oral bioavailability and poor selectivity on SGLT2 enzymes and many adverse effects including dehydration, diarrhea, and abnormal growth of muscle and bone (Takasu et al. 2019; Ehrenkranz et al. 2005). Currently prescribed synthetic SGLT2 inhibitors, canagliflozin (**174**), dapagliflozin (**175**), and empagliflozin (**176**) are used for treatment of type 2 diabetes in combination with other oral hypoglycemic drugs and effective in lowering of blood glucose, blood pressure, and body weight gain. However, the long-term use of these SGLT2 inhibitors in diabetic patients is associated with adverse side effects including female genital mycotic infections, urinary tract infections, increased urination, moderate to severe renal dysfunction, and diabetic ketoacidosis (DKA). The DKA develops extensively the states of low blood glucose levels (Hsia et al. 2017; Plodkowski et al. 2015; Halimi and Verges 2014). Some natural products have been reported to possess strong inhibitory effect against SGLT2 activity. These natural products could be utilized as an alternative to synthetic SGLT2 inhibitors for treatment of diabetes. For instance, two picraline-type alkaloids, 10-methoxy-N(1)-methylburnamine-17-O-veratrate (**177**) and alstiphyanine D (**178**) from antidiabetic plant, *Alstonia macrophylla*, strongly inhibited the activity of SGLT2 with IC_{50} of 0.5 and 2.0 μM and of SGLT1 with IC_{50} of 4.0 and 5.0 μM, respectively (Arai et al. 2010). Four flavonoids, (-)-kurarinone (**179**), sophoraflavanone G (**180**), isoflavone glycosides A (181) and B (**182**), from the roots of Chinese herb, *Sophora flavescens*, showed strong to moderate inhibitory effect on the activity of SGLT2 with IC_{50} of 1.7, 4.1, 2.6, and 15.3 μM, respectively (Sato et al. 2007b; Yang et al. 2015a). Two stilbene trimers, gneyulins A (**183**) and B (**184**) from *Gnetum gnemonoides*, showed moderate inhibitory effect against SGLT2 with IC_{50} of 25.0 and 18.0 μM and SGLT1 with IC_{50} of 27.0 and 37.0 μM, respectively (Shimokawa et al. 2010). Two cyclic diarylheptanoids, acerogenin-A (**185**) and B (**186**) from the bark of Japanese plant, *Acer nikoense*, showed moderate inhibitory effect against SGLT1 with IC_{50} of 20 and 26 μM and weak effect against SGLT2 with IC_{50} of 94 and 43 μM, respectively (Morita et al. 2010).

4.7.5 Inhibition of DPP4 Activity

Dipeptidyl peptidase-4 (DPP4), also known as cluster of differentiation-26 (CD26), is an exopeptidase glycoprotein, released from differentiated adipocytes and expressed in a variety of tissues including the pancreas, liver, and adrenal glands and exerts paracrine and endocrine effects in cell signaling and insulin action. It is expressed in high concentrations on plasma of obese and diabetic patients. DPP4 selectively cleaves N-terminal dipeptides from a variety of substrates including cytokines, growth factors, neuropeptides, and incretin hormones, GLP-1 and GIP. It is responsible for deactivation of incretin hormones and to reduce postprandial insulin secretion, resulting in decreased plasma insulin and elevated plasma glucose levels in obese and diabetic patients. It represents a molecular link between obesity and vascular dysfunction (Rohrborn et al. 2015; Drucker and Nauck 2006; Drucker 2006). A recent study reported that significantly high plasma DPP4 levels in obese and nonobese diabetic patients are positively correlated with fasting plasma insulin, HbA1c (above 9.0%), LDL-C levels, triceps skinfolds and intra-abdominal adiposity, and waist to hip ratio (Anoop et al. 2017). Incretin (insulin action potentiation) hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) are secreted from gut (small intestine) endocrine L- and K-cells after a meal intake to stimulate insulin secretion from pancreatic β-cells and to suppress glucagon secretion from pancreatic α-cells, to inhibit gastric emptying in stomach and reduce food intake and elevated serum glucose and HbA1c levels (Drucker 2006). Both GLP-1 and GIP exert their action through their G-protein coupled receptors, GLP-1R, GIPR, that are expressed in β-cells to increase the levels of cAMP and intracellular Ca^{2+} and insulin exocytosis in a glucose-dependent manner. Moreover, GLP-1R promotes insulin biosynthesis and β-cell proliferation and inhibits β-cell apoptosis (Drucker 2006). Therefore, inhibition of DPP4 activity is a promising therapeutic target for reduction of hyperglycemia in obese and diabetic patients. Currently some DPP4 inhibitors, namely, sitagliptin, saxagliptin, linagliptin, vildagliptin, alogliptin, anagliptin, gemigliptin, and teneligliptin (**188**–**195**), are widely prescribed in combination with other oral hypoglycemic agents for treatment of hyperglycemia in type 2 diabetic patients. Most of these DPP4 inhibitors (DPP4i) improve hyperglycemia, cardiovascular function, and aortic lesions in diabetic patients. However, about 5% or more of patients receiving these DPP4i have reported some adverse effects including upper respiratory tract infection, nasopharyngitis, headache, and skin lesions during the treatment period (Dicker 2011; Pathak and Bridgeman 2010). Various types of phytochemicals from fruits, vegetables, plants, edible seaweeds, and mushrooms have been reported to have potential inhibitory effect on DPP4 activity. These phytochemicals or their parent extracts could be useful for diabetes treatment as DPP4 inhibitors after clinical trials in humans. For example, resveratrol (**47**) from grape fruit, genistein (**96**) from soybean, flavonoids luteolin (**196**), apigenin (**197**), quercetin (**23**), kaempferol (**66**), hesperetin (**198**), naringenin (**199**) from citrus fruits, and anthocyanins cyanidin-3-glucoside (**31**), cyanidin, and malvidin from blueberry and blackberry showed strong inhibitory effect against DPP4 activity with IC_{50} of 0.0006, 0.048,

0.12, 0.14, 2.92, 0.49, 0.28, 0.24, 0.42, 1.41, and 1.41 μM, respectively (Fan et al. 2013). Emodin (**123**) from *Rheum palmatum*, eriodictyol (**200**), hispidulin (**201**) from Mexican oregano (*Lippia graveolens*), cirsimaritin (**202**), and rosmarinic acid **104** from rosemary (*Rosmarinus officinalis*) strongly inhibited the activity of DPP4 with an IC_{50} value of 5.76, 10.9, 0.49, 0.43, and 14.1 μM, respectively (Wang et al. 2017e; Bower et al. 2014). Cyanidin-3,5-diglucoside (**203**) from aronia berries (*Aronia melanocarpa*), berberine (**48**) from *Coptis chinensis*, aqueous leaf extract of tulsi (*Ocimum sanctum*), and tripeptides, diprotins A (**204**) and B (**205**) from bacterium *Bacillus cereus* BMF 673-RF1 showed strong inhibitory effect against the activity of DPP4 with IC_{50} of 5.5 μM, 13.3 μM, 0.38 μg/ml, 1.1 μg/ml, and 5.5 μg/ml, respectively (Kozuka et al. 2015; Al-Masri et al. 2009; De et al. 2015; Umezawa et al. 1984).

4.7.6 Inhibition of PTP1B Activity

Insulin resistance is a hallmark of type 2 diabetes and diet-induced obesity. The protein tyrosine phosphatase 1B of family protein tyrosine phosphatases and plays a key role as negative regulator of both insulin and leptin signaling for development of insulin and leptin resistance in obesity and type 2 diabetes. In insulin signaling, insulin on binding to its receptor IR promotes phosphorylation of IR, IRS, and Akt sequentially in peripheral tissues including the skeletal muscle, liver, and adipose tissue for glucose metabolism and utilization, while PTP1B negatively regulates the insulin signaling through dephosphorylation of phosphorylated IR and IRS. In HFD-fed obese mice, PTP1B on overexpressions in arcuate nucleus of hypothalamus in mice brain negatively regulates leptin signaling through dephosphorylation of Janus kinase 2 (JNK2) to increase the storage of fat mass in the body by increasing leptin resistance in the hypothalamus. PTP1B-deficient mice are more sensitive to insulin in the insulin-sensitive tissues, muscle, and liver and improve hyperglycemia in type 2 diabetes and fat metabolism in diet-induced obesity (Elchebly et al. 1999; Valverde and Gonzalez-Rodriguez 2011). In skeletal muscle of type 2 diabetic African Americans, overexpression of PTP1B proteins reduces the level of Akt phosphorylation and decreases insulin-stimulated glucose uptake and glucose metabolism. While, reduction of PTP1B expression by transfection with PTP1B siRNA vector increases the insulin-stimulated phosphorylation level of Akt in primary human skeletal muscle culture (HSMC), collected from the subjects with type 2 diabetes (Stull et al. 2012). Another study on PTP1B enzymes reported that in high-fat fed mice, the expression of PTP1B in the adipose tissue, muscle, liver, and arcuate nucleus of hypothalamus was increased by 1.5- to 7-folds and was positively correlated with increased expression of macrophage marker CD68 and TNFα in adipose tissue. Moreover, TNFα treatment in 3T3-L1 adipocyte and H4IIE hepatocyte culture increased the expression of PTP1B mRNA and protein levels by 2-to 5-folds. It suggested that overexpression of PTP1B enzymes in multiple tissues in obesity is regulated by inflammation (Zabolotny et al. 2008). It is also observed that the protein silent information regulator 1 (SIRT1) on overexpression or activation in

insulin resistant conditions reduces the expression levels of PTP1B mRNA and proteins and improves insulin sensitivity by increasing insulin stimulated phosphorylation of IR, IRs, and Akt by suppression of inflammation and improvement of antioxidant activity in the liver and skeletal muscle of obese mice (Sun et al. 2007). Therefore, inhibition or downregulation of PTP1B activity for improvement of insulin signaling pathway is a potential target for treatment of type 2 diabetes and diet-induced obesity. Various classes of phytochemicals from plants, seaweeds, fungi, and marine animals improved insulin resistance in obesity and type 2 diabetes by inhibition of PTP1B expression and activity (Table 4.2) (Wang et al. 2015b; Zhao et al. 2018a). These natural products could be utilized as diet supplement for treatment of both obesity and diabetes. For example, triterpenes ursolic acid (**52**) and corosolic acid (**206**) from *Symplocos paniculata* inhibited the activity of PTP1B in a competitive manner with IC_{50} of 3.8 and 7.2 μM, respectively (Na et al. 2006). Triterpenes, betulinic acid (**207**) from *Saussurea lappa*, tormentic acid (**208**) and palmitic acid (**209**) from *Agrimonia pilosa*, hopane-6α, 22-diol **210** from *Lecidella carpathica* inhibited the activity of PTP1B with IC_{50} of 0.70 μg/ml, 0.50 μM, 0.10 μm, and 3.7 μM, respectively (Choi et al. 2009; Na et al. 2016; Seo et al. 2011). Flavonols, isorhamnetin (**211**), isorhamnetin-3-*O*-β-D-glucoside (**212**), isorhamnetin-3-*O*-β-D-rutinoside (**213**) and quercetin (**23**) and three triterpenes, 2α, 3β-dihydroxy-olean-12-en-23, 28,30-trioic acid (**214**), sorghumol (**215**), and epifriedelanol (**216**) from *Anoectochilus chapaensis* exhibited strong inhibitory effect against hPTP1B protein with IC_{50} of 1,75, 1.16, 1.20, 5.63, 2.65, 3.50, and 3.75 μM, respectively (Cai et al. 2015). The chalcones, xanthoangelol K (**217**); xanthoangelol (**218**), xanthoangelols D (**219**), E (**220**), and F (**221**); 4-hydroxyderricin (**222**) from *Angelica keiskei* inhibited the activity of PTP1B with IC_{50} of 0.82, 1.97, 3.97, 1.43, 1.67, and 2.47 μg/ml, respectively (Li et al. 2015). Flavonoids, albafurans A (**223**) and B (**224**) from *Morus alba* var. *tatarica*, and kuwanons J (**225**), R (**226**), and V (**227**) from *Morus bombycis* inhibited the activity of PTP1B with IC_{50} of 7.9, 8.9, 2.7, 8.2, and 13.8 μM, respectively (Zhang et al. 2014a; Hoang et al. 2009). Naphthoquinones, deoxyshikonin (**228**), shikonin (**229**), acetylshikonin (**230**), and β,β′-dimethylacrylalkannin (**231**) from *Arnebia euchroma* strongly inhibited the activity of PTP1B with IC_{50} value of 0.80, 4.42, 1.02, and 0.36 μM, respectively (Wang et al. 2016a). Prenylated isoflavones, angustone A (**232**), isoangustone A (**233**) from *Glycyrrhiza uralensis*, alkaloid papaverine (**234**) from *Papaver somniferum*, and gallotannin, 1,2, 3,4,6-penta-*O*-galloyl-D-glucopyranose (**235**), from *Paeonia lactiflora* inhibited the activity of PTP1B with IC_{50} of 0.4, 3.0, 1.20, and 4.8 μM, respectively (Ji et al. 2016; Bustanji et al. 2009a; Baumgartner et al. 2010). Four quinic acid derivatives, 3,4-dicaffeoylquinic acid (**236**), 3,5-dicaffeoylquinic acid (**237**), 3,5-dicaffeoylquinic acid methyl ester (**238**), and 4,5-dicaffeoylquinic acid (**239**) from *Artemisia capillaris* showed strong inhibitory effect against PTP1B with IC_{50} value of 2.60, 2.02, 2.99, and 3.21 μM, respectively (Islam et al. 2013). Phytochemicals, asperentin B (**240**) from marine fungus, *Aspergillus sydowii*, tanzawaic acids A (**241**) and B (**242**) from fungus *Penicillium* sp. SF-6013, anhydrofulvic acid (**243**) and penstyrylpyrone (**244**) from *Penicillium* sp. JF-55,

and aquastatin A (**245**) from marine fungus *Cosmospora* sp. SF-5060, inhibited the activity of PTP1B with IC_{50} of 2.05, 8.2, 8.2, 1.90, 5.28, and 0.19 μM, respectively (Wiese et al. 2017; Quang et al. 2014; Lee et al. 2013a; Seo et al. 2009). Phlorotannins, eckol (**164**), dieckol (**163**), 7-phloroeckol (**246**), and phlorofurofucoeckol-A (**167**) from marine brown algae, *Ecklonia stolonifera* and *Eisenia bicyclis*; carotenoid fucoxanthin (**158**) from marine alga, *Undaria pinnatifida*; thunberol (**247**) from brown alga, *Sargassum thunbergii*; racemosin C (**248**) and caulersin (**249**) from marine green alga *Caulerpa racemosa*; and caulerpin (**250**) from *Caulerpa taxifolia* strongly inhibited the activity of PTP1B with an IC_{50} value of 2.64, 1.18, 2.09, 0.56, 4.80, 2.24, 5.86, 7.14, and 3.77 μM, respectively (Moon et al. 2011; Jung et al. 2012b; He et al. 2014; Yang et al. 2014a; Mao et al. 2006). Phytochemicals, such as sesquiterpene quinones, frondophysin A (**251**) from marine sponge *Dysidea frondosa*, dysidine (**252**) from *Dysidea villosa*, and stellettin G (**253**) from marine sponge *Stelleta* sp. exhibited inhibitory effect against PTP1B activity with IC_{50} of 0.39, 1.5, and 4.1 μM, respectively (Jiao et al. 2019; Zhang et al. 2009; Xue et al. 2013).

4.7.7 Inhibition of 11β-HSD1 Activity

The enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1), a negative regulator of insulin signaling pathway, is overexpressed in the liver, adipose tissue, gonad, and brain in obese humans and rodents and actively regulates the function of glucocorticoids in these tissues by conversion of inactive cortisone into active cortisol in presence of NADPH. Emerging evidence demonstrates that high-fat-fed transgenic mice overexpressing 11β-HSD1 in adipose tissue increases visceral obesity, insulin resistance, hyperglycemia, hyperlipidemia, and hyperphagia. Moreover, overexpression of 11β-HSD1 in adipose tissue promotes adipocyte differentiation and upregulated the expression of leptin, LPL, and TNFα in adipocytes and increases lipid accumulation in abdominal lesion, and in the liver, it promotes gluconeogenesis through upregulation of the expression of PEPCK. It also reduces energy expenditure by decreasing the expression of thermogenic gene UCP1 in interscapular BAT (Masuzaki et al. 2001). 11β-HSD1-deficient mice markedly reduced hyperglycemia and hyperlipidemia by decreasing the levels of plasma TG, LDL-C, FFAs, and glucose and increased insulin sensitivity in the liver and adipose tissue by decreasing hepatic glucose production and increasing fat metabolism through downregulation of PEPCK and G6Pase and upregulation of CPT1, ACOX, PPARα, and UCP2 (Morton et al. 2001; Kotelevtsev et al. 1997). Moreover, high-dose cortisol administration maintaining pituitary-pancreatic (P-P) infusion protocol in humans increased plasma glucose, leucine, and phenylalanine levels by stimulating gluconeogenesis in the liver and proteolysis in skeletal muscle. These results suggest that cortisol reduces insulin action in liver and muscle in human subjects (Khani and Tayek 2001; Brillon et al. 1995). Therefore, inhibition of 11β-HSD1 activity is a potential strategy to improve insulin action in treatment of obesity and diabetes. Usually transfected HEK293 cells are used for the assay of

human and rodent 11β-HSD1 activity in cellular model. Various phytochemicals and plant extracts have been reported as potent inhibitors of 11β-HSD1 activity, and these natural products could be utilized in the development of natural antidiabetic medicines. Among these phytochemicals, emodin (**123**), aloe-emodin (**123a**), and rheochrysidin (**254**) from *Rheum palmatum* rhizomes inhibited the activity m (mouse)-11β-HSD1 with IC_{50} of 86, 98, and 81 nM and of human (h)-11β-HSD1 with IC_{50} of 186, 879, and 542 nM, respectively (Feng et al. 2010). Curcumin **9** from *Curcuma longa* rhizome strongly inhibited the activity of h-and m-11β-HSD1 with IC_{50} of 2.29 and 5.79 μM, respectively, in a competitive manner (Hu et al. 2013). Triterpene cochinchinoid K **255** from Vietnamese *Walsura cochinchinensis* herb showed strong inhibitory effect against m-11β-HSD1 with an IC_{50} of 0.82 μM (Han et al. 2013). Tirrucallane-type triterpene, 22*S*,23*R*-epoxytirrucalla-7-ene-3α,24,25-triol (**256**), from *Walsura robusta* leaves strongly inhibited the activity of human and mouse 11β-HSD1 with IC_{50} of 1.9 and 1.2 μM, respectively, while other three triterpenes from the same plant, niloticin (**256a**), dihydroniloticin (**256b**), and piscidinol A (**256c**) strongly inhibited the activity of mouse 11β-HSD1 with IC_{50} of 0.69, 3.8, and 0.88 μM, respectively (Wang et al. 2016). Ursane-type triterpenes, ursolic acid (**52**), corosolic acid (**206**), 3-epicorosolic acid methyl ester (**257**), tormentic acid methyl ester (**258**) and 2α-hydroxy-3-oxo-urs-12-en-28-oic acid (**259**), 11-keto-ursolic acid (**260**), and 3-acetyl-11-keto-ursolic acid (**261**) from an antidiabetic plant, *Eriobotrya japonica*, showed strong inhibitory effect against 11β-HSD1 with IC_{50} value of 1.9, 0.81, 5.2, 9.4, 17, 2.06, and 1.35 μM, respectively (Rollinger et al. 2010). Triterpene of ursane-type, isoyarumic acid (**262**) from Latin American *Cecropia telenitida* strongly inhibited the activity of 11β-HSD1 with IC_{50} of 0.95 μM (Mosquera et al. 2018). Limonoids, dysoxylumosin F (**263**) from *Dysoxylum mollissimum* twigs (red bean) and harperforin G (**264**) from Thai *Harrisonia perforata*, showed potent inhibitory effect against h-11β-HSD1 with an IC_{50} of 9.6 nM and 0.58 μM, respectively (Zhou et al. 2015; Yan et al. 2016). Two steroids, masticadienonic acid (**265**) and isomasticadienonic acid (**266**) from *Pistacia lentiscus* (mastic gum), exhibited strong inhibitory effect against 11β-HSD1 with IC_{50} of 2.51 and 1.94 μM, respectively (Assimopoulou et al. 2015). Phenolics, 6-paradol (**152**), 6-shogaol (**153**), and (5*R*)-acetoxy-6-gingerol (**267**) from white ginger, *Zingiber officinale*, rhizomes showed potent inhibitory effect against h-11β-HSD1 with IC_{50} in the range of 1.09–1.30 μM (Feng et al. 2011). A catechin derivative, EGCG (**35**), from green tea showed moderate inhibitory effect against h-11β-HSD1 with an IC_{50} of 57.99 μM (Hintzpeter et al. 2014). A cyclic tetrapeptide, penicopeptide A (**268**) isolated from the culture of endophytic fungus *Penicillium commune* of grape plant, *Vitis vinifera*, in rice, inhibited the activity of h-11β-HSD1 with an IC_{50} of 9.07 μM (Sun et al. 2016).

4.7.8 Inhibition of Aldose Reductase (AR) Activity

Aldose reductase (AR) (alditol: NADP oxidoreductase EC.1.1.1.21), an enzyme of aldo-keto reductase superfamily, catalyzes the conversion of glucose into sorbitol in

presence of NADPH in the polyol pathway under hyperglycemic condition in diabetes. Sorbitol is a membrane-impermeable substance, and its accumulation in cells increases osmotic stress. Sorbitol is further metabolized into fructose by sorbitol dehydrogenase (SDH), and fructose, in turn, is metabolized into dicarbonyl compounds, 3-deoxyglucosone (3-DG) and methyl glyoxal (MG), which are recognized as potent glycating agents and participate in the formation of advanced glycation end products (AGEs). Moreover, in the process of conversion of glucose into fructose under high glucose concentrations, in the first step, AR utilizes NADPH and consequently reduces GSH level, and in the second step, SDH utilizes cofactor NAD+ for conversion of sorbitol into fructose and thereby converts NAD+ into NADH, which is a substrate of NADH oxidase, leading to the production of superoxide anions. Further, AR on overexpression induces oxidative stress-induced inflammation via activation of PKC and NFκB in different tissues, particularly in the heart, retina, and kidney. Accumulation of sorbitol in different tissues under hyperglycemic conditions leads to secondary diabetic complications, such as diabetic cataractogenesis, retinopathy, neuropathy, myocardial infarction, and nephropathy (Brownlee 2001). Accumulating evidence demonstrates that human eye lens-specific overexpression of AR accelerates high-glucose-induced cataract via apoptosis of lens epithelial cells through stimulation of TNFα-induced activation of PKC and NFκB (Ramana et al. 2003). Treatment of AR inhibitor, tolrestat or sorbinil, or transfected AR siRNA in high-glucose exposed vascular smooth muscle cells (VSMCs) prevented the activation of PKC and formation of diacylglycerol (DAG) (Ramana et al. 2005). Moreover, inhibition of AR activity markedly protects both diabetic and nondiabetic rat hearts from ischemic injury via reduction of cystolic NADH/NAD+ ratio and creatine kinase production, and increased ATP production (Ramasamy et al. 1997). Various natural products have been shown strong in vitro inhibitory effects against rat lens AR (RLAR). These natural products could be useful in treatment of diabetic complications. The properties of RLAR are similar to those of human placental AR (HPAR), and these natural RLAR inhibitors would be effective against human AR. For example, flavonoids, quercetin (**23**) and luteolin **196** and its glycoside, scolymoside (**269**), apigenin (**197**), isoquercitrin (**270**), and hyperoside (**271**), and phenolic acids, chlorogenic acid (**21**) and 3,5-di-*O*-caffeoylquinic acid (**237**) from *Artemisia montana*, strongly inhibited the activity of RLAR with IC_{50} of 0.30, 0.19, 0.55, 0.67, 1.16, 1.85, 4.36, and 5.37 μM, respectively (Jung et al. 2011). Five gallotannins, 1,2,3-tri-*O*-galloyl-β-D-glucose (**272**), 1,2,3,6-tetra-*O*-galloyl-β-D-glucose (**273**), 1,2,4,6-tetra-*O*-galloyl-β-D-glucose (**274**), 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose (**235**), and tellimagrandin (**275**) from *Cornus officinalis* seeds inhibited the activity of RLAR with IC_{50} values of 2.35, 0.70, 0.76, 1.93, and 0.90 μM, respectively (Lee et al. 2011c). Flavanone myrciacitrin I (**276**), flavonol glycosides myricitrin (**92**), mearnsitrin (**277**), quercitrin (**122**), desmanthin I (**278**), and guaijaverin (**279**) from *Myrcia multiflora* leaves inhibited the activity of RLAR with IC_{50} values of 3.2, 3.8, 1.4, 0.15, 0.082, and 0.18 μM, respectively (Yoshikawa et al. 1998). Diterpenes danshenols A (**280**) and B (**281**), dihydrotanshinone I (**282**), tanshinone IIA (**283**), and danshexinkun A (**284**) from *Salvia miltiorrhiza* root showed moderate to strong inhibitory effect

against RLAR with IC_{50} of 0.10, 1.75, 1.19, 1.14, and 0.87 μM, respectively (Tezuka et al. 1997). Phenolic acids, lithospermic acid B (**285**), salvianolic acid K (**286**), salviaflaside (**287**), and rosmarinic acid (**104**) from *Salvia deserta* showed moderate inhibitory effect against RLAR with IC_{50} of 2.63, 2.81, 3.15, and 3.91 μM, respectively (Kasimu et al. 1998). Three quinic acid derivatives, 3-caffeoylquinic acid (**288**), 3,5-di-*O*-caffeoylquinic acid (**237**), and 3,5-di-*O*-caffeoyl-*epi*-quinic acid (**289**) from *Erigeron annuus* inhibited the activity of RLAR with IC_{50} of 1.67, 0.79, and 0.44 μM, respectively (Jang et al. 2010). Isoflavonoids tectorigenin (**290**), tectoridin-4'-*O*-β-D-glucoside (**291**), and kakkalide (**292**), from *Viola hondoensis* and tectoridin (**293**) from *Belamcanda chinensis* inhibited the activity of RLAR with IC_{50} of 1.12 μM, 0.54 μM, 0.34 μg/ml and 1.08 μM, respectively (Moon et al. 2006; Chung et al. 2008; Jung et al. 2002). Isoflavonoids, semilicoisoflavone B (**294**), liquiritigenin (**94**), and isoliquiritigenin (**295**), from *Glycyrrhiza uralensis* roots inhibited the activity of RLAR and human recombinant (hr)-AR with IC_{50} of 1.8, 2.0, 3.4 μM, and 10.6, 21.9, 27.5 μM, respectively (Lee et al. 2010b). Four biflavonoids, chamaejasmin (**296**), 7-methoxyneochamaejasmin (**297**), 7-methoxychamaejasmin (**298**), and chamaejasmenin B (**299**), and a chromone, chamaechromone (**300**), from *Stellera chamaejasme* inhibited the activity of RLAR with IC_{50} of 1.8, 2.9, 4.1, 5.9, and 7.4 μM, respectively (Feng et al. 2005). A *C*-glycosidic flavonoid derivative, swertisin (**301**), from *Enicostemma hyssopifolium* inhibited the activity of RLAR with an IC_{50} of 1.6 μM (Patel and Mishra 2009). Flavonoids, isoorientin (**302**), vitexin (**303**), luteolin-6-*C*-(6"-*O*-*trans*-caffeoylglucoside) (**304**), tricin (**305**), and p-coumaric acid (**19**) from black bamboo, *Phyllostachys nigra*, leaves, showed strong to moderate inhibitory effect against the activity of RLAR with IC_{50} of 1.91, 2.03, 0.013, 2.03, and 0.14 μM, respectively (Jung et al. 2007). Flavonoid isorhamnetin-3-O-β-D-glucoside (**212**) from *Salicornia herbacea* inhibited the activity of RLAR with an IC_{50} of 1.4 μM (Lee et al. 2005b). Two flavonoids compounds, chalcone butein (**306**) and aurone sulfuretin (**307**), from Asian *Rhus verniciflua* bark showed strong inhibitory effect against RLAR with IC_{50} of 0.7 and 1.3 μM, respectively (Lee et al. 2008a). Three acylated flavanone glycosides, matteuorienates A (**308**), B (**309**), and C (**310**) from Chinese *Matteuccia orientalis* rhizomes, exhibited strong inhibitory effect against RLAR with IC_{50} values of 1.0, 1.0 and 2.3 μM, respectively (Kadota et al. 1994). Leuteolin and its glycosides, luteolin-7-O-β-D-glucopyranoside (**311**), luteolin-7-O-β-D-glucopyranosiduronic acid (**312**), (2*S*)-and (2*R*)-eriodictyol-7-O-β-D-glucopyranosiduronic acids (**313**), (**314**) from *Chrysanthemum indicum* flowers showed moderate inhibitory effect against RLAR with IC_{50} of 0.45, 0.99, 3.1, 2.1, and 1.5 μM, respectively (Yoshikawa et al. 1999; Matsuda et al. 2002). Two anthocyanins, delphinidin-3-*O*-β-galactopyranoside-3'-β-glucopyranoside (**315**) and delphinidin-3-*O*-β-galactopyranoside-3',5'-di-*O*-β-glucopyranoside (**316**) from *Litchi chinensis* fruits exhibited strong inhibitory effect against RLAR with IC_{50} of 0.23 and 1.23 μM, respectively (Lee et al. 2009). Phenolic aldehyde, protocatechualdehyde (**317**), from mushroom *Ganoderma applanatum* showed strong inhibitory effect against RLAR with IC_{50} of 0.7 μM (Lee et al. 2005a). Hispidin dimers, davallialactone (**318**), hypholomine B (**319**), and ellagic acid

(**320**), from medicinal mushroom *Phellinus linteus* showed potent inhibitory effect against both RLAR and hrAR with IC_{50} values of 0.33, 0.82, and 0.63 μM and of 0.56, 1.28, and 1.37 μM, respectively (Lee et al. 2008b). A bromophenol, rubrolide L (**321**), from marine tunicate *Ritterella rubra*, and lukianol B (**322**) from an unidentified Pacific tunicate, showed strong inhibitory effect against hAR2 with IC_{50} of 0.8 and 0.6 μM, respectively (Manzaro et al. 2006). A diphenyl aldostatin analog, WF-2421 (**323**), from fungus *Humicola grisea* showed strong inhibitory effect against rabbit lens AR with IC_{50} of 0.03 μM (Nishikawa et al. 1991).

4.7.9 Stimulatory Effect on TGR5 Activation

The membrane protein, Takeda G-protein receptor 5 (TGR5), also known as G-protein-coupled bile acid receptor 1 (GPBAR1) or membrane-type receptor for bile acid (M-BAR) mediates the physiological functions of bile acids. The membrane protein, TGR5 is expressed in the liver, brown adipose tissue, pancreas, intestine, and spleen and plays a key role in glucose and energy metabolism for maintenance of glucose and energy homeostasis in obesity and diabetes (Maruyama et al. 2006; Chen et al. 2011). Bile acids (BAs), such as cholic acid (CA **324**) and chenodeoxycholic acid (CDCA **325**) are the primary BAs that are synthesized in hepatocytes and transported into gallbladder for storage. BAs are secreted in small intestine in response to dietary intake for its emulsification as dietary lipids for absorption (Russell 2003). In vitro, TGR5 is endogenously expressed in enteroendocrine cells, such as human NCI-H716, mouse STC-1 and GLUTag cell lines, suggesting its potential role in intestine (Maruyama et al. 2002). TGR5 on activation by BAs increases energy expenditure in BAT through upregulation of intracellular cAMP and activation of the enzyme type 2 iodothyronine deiodinase (D2, also known as Dio2) for conversion of thyroxine (T4) to tri-iodothyronine (T3) and T3-induced upregulation of thermogenin gene, UCP1 via BAs/TGR5/cAMP/D2/T3/UCP1 signaling pathway (Watanabe et al. 2006). TGR5 activation increases the secretion of incretin GLP-1 from intestinal endocrine L-cells and promotes insulin action in the liver and muscle of obese mice and induces mitochondrial oxidative phosphorylation in amelioration of obesity-associated nonalcoholic steatohepatitis (NASH) (Thomas et al. 2009). TGR5 on activation protects high-glucose-induced cardiomyocyte injury by improving antioxidant status via upregulation of Nrf2 and HO-1 expression and improves diabetic retinopathy through upregulation of tight junction protein ZO-1 via suppression of TNF-α-induced RhoA/RhoA-associated coiled-coil containing protein kinase (ROCK) signaling pathway in human retinal microvascular endothelial cells (RMECs) (Deng et al. 2019a; Zhu et al. 2020). Therefore, the stimulation of TGR5 activity is a promising target for treatment of obesity and diabetes. Some natural products have been reported as potent TGR5 agonists. For example, oleanolic acid (**326**) from *Olea europaea* leaves acts as potential TGR5 agonist and improves insulin sensitivity in liver of HFD-fed obese mice by upregulation of IRS and suppression of FoxO1 activity and expression of gluconeogenic genes, PEPCK and G6Pase. Moreover, it

increases insulin secretion in pancreatic β-cells through promotion of stimulus-secretion coupling (SSC), activation of adenylyl cyclase (AC), increased accumulation of intracellular Ca^{2+} ions, cAMP production, and activation of protein kinase A (PKA) in a AC/cAMP/PKA pathway (Sato et al. 2007a; Maczewsky et al. 2019). In cellular model, the TGR5 agonistic activity of natural products is evaluated by measuring intracellular cAMP production in Chinese hamster ovary (CHO-K1) cells or human NCI-H716 cells or HEK293 cells transfected with human TGR5 cDNA plasmid (siRNA) gene in a cAMP response element (CRE)-luciferase assay using BAs as positive control (Lo et al. 2016). In addition to primary BAs, CA and CDCA, secondary BAs, lithocholic acid (LCA **327**), and deoxycholic acid (DCA **328**), formed by bacterial dehydroxylation in humans, are used as positive control. Two synthetic BAs, 6α-6-ethyl-23*S*-methyl-cholic acid (EMCA, INT-777) and taurolithocholic acid (TLCA **329**), are also used as positive control. Natural betulinic acid (**207**), oleanolic acid (**326**), and ursolic acid (**52**) exhibited strong TGR5 agonistic activity, similar to bile acids with EC_{50} of 1.04, 2.25 and 1.43 μM, respectively, in NCI-H716 cells. Moreover, betulinic acid in TGR5 receptor transfected CHO-K1 cells, increased glucose uptake and insulin secretion through increased intracellular cAMP level and PKA activity, and this effect was blocked on treatment of triamterene, an antagonist of PKA in the cell culture (Genet et al. 2010; Lo et al. 2016). Another study reported that four triterpene acids, oleanolic acid (**326**), maslinic acid (**330**), corosolic acid (**206**), and ursolic acid **52** from allspice (*Pimenta dioica*) unripe fruits and clove (*Syzygium aromaticum*) flower buds, showed TGR5 agonistic activity with EC_{50} of 2.2, 2.7, 0.5, and 1.1 μM, respectively in CRE-luciferase assay (Ladurner et al. 2017). Imperatorin (**331**), a furocoumarin present in many plants including *Angelica dahurica*, acts as TGR5 agonist by increasing glucose uptake in CHO-K1 cells transfected with TGR5 gene. In NCI-H716 cells, it increased intracellular Ca^{2+}-concentration and GLP-1 secretion, and these effects were blocked by triamterene treatment. Moreover, in type 2 diabetic rats, it increased plasma GLP-1 level (Wang et al. 2017a). Nomilin (**332**), present as a major limonoid constituent in many citrus seeds including *Citrus aurantium* and *C. reticulata*, showed strong TGR5 agonistic activity in h-TGR5-transfected HEK293 cell line culture with EC_{50} of 23.6 μM, compared to that of positive control, TLCA of EC_{50} of 1.37 μM, and weak activity for mTGR5 (EC_{50} of 46.2 μM). In silico docking study, it showed good binding interaction with h-TGR5 protein receptor through hydrogen bonding with three amino acid residues, Q77, R80, and Y89 via carbonyl oxygen and furan oxygen functions. Moreover, nomilin on treatment in HFD-fed obese mice reduced body weight gain and serum glucose and insulin levels and enhanced glucose tolerance in obese mice via upregulation of insulin secretion and lipid metabolism (Sasaki et al. 2017; Ono et al. 2011). Sesquiterpene coumarins, farnesiferol B (**333**) and microlobidene (**334**) from *Ferula assa-foetida*, showed TGR5 agonistic activity with EC_{50} of 13.53 and 13.88 μM, respectively, in HEK293 cells transfected with hTGR5 transmid gene (Kirchweger et al. 2018). Alkaloids coptisine (**129**), berberine (**48**), and palmatine (**130**) from *Rhizoma coptidis* enhanced the activity of BAs receptors, FXR and TGR5, in diet induced obese mice to ameliorate hyperlipidemia in mice by suppression of GOT-2

expression and upregulation of mitochondrial function in oxygen consumption and fatty acid oxidation (He et al. 2016).

4.7.10 Inhibition of GSK-3 Activity

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase and exists in two isoforms, GSK-3α and GSK-3β, with two distinct genes and both these genes have overlapping roles in the development of human diseases including obesity, type 2 diabetes, neurodegenerative disorders, such as Parkinson disease, Alzheimer disease, and bipolar disorders and cancers (Hansen et al. 1997; Eldar-Finkelman 2002). GSK-3 on overexpression in the skeletal muscle of type 2 diabetic humans promotes the phosphorylation of insulin receptor substrate-1 (IRS-1) at ser 332 site and inhibits the activity of insulin for tyrosine phosphorylation of IRS-1 and thereby causes insulin resistance in type 2 diabetes. The mutation of ser 332 site of IRS-1 enhances insulin-induced tyrosine phosphorylation of IRS-1 (Eldar-Finkelman and Krebs 1997; Liberman and Eldar-Finkelman 2005). Moreover, GSK-3, on overexpression in the skeletal muscle of obese rodents and type 2 diabetic humans impairs insulin stimulated glucose uptake and glycogen synthesis and in the liver increases the glucose production by upregulation of gluconeogenic gene PEPCK. In the skeletal muscle, GSK-3 phosphorylates glycogen synthase (GS) on three specific residues and thereby causes deactivation of GS and inhibits the activity of GS on glucose-6-phosphate in glycogen synthesis. Insulin-stimulated phosphorylated protein kinase B (PKB), also known as Akt or Rac, inhibits the activity of GSK-3 by promoting the phosphorylation at ser 21 in GSK-3α and ser 9 in GSK-3β to stimulate glucose uptake in skeletal muscle via upregulation of GLUT4 translocation into cell membrane and to increase glycogen synthesis via increasing the activity of GS by dephosphorylation and to reduce hepatic glucose production by decreasing the expression of gluconeogenic genes (Cross et al. 1995). Human muscle cell selective inhibitors of GSK-3, namely, lithium chloride and INHs (CHIR98014 and CHIR98023), in human diabetic muscle cells exhibit insulin-like effects on glucose metabolism by increasing glucose uptake and glycogen synthesis. In addition, these GSK-3 inhibitors in obese type 2 diabetic rodents and humans increase glycogen synthesis in skin and adipocytes and reduce hepatic glucose production and decrease hyperphosphorylation of tau proteins and neuronal apoptosis in the brain. Treatment of GSK-3β inhibitor, AR-AO14418 or TX14 (A), in diabetic mice improved the learning deficit in mice by upregulation of synaptophysin, a marker of hippocampal plasticity and preventing the activity of GSK-3β in the brain (Nikoulina et al. 2002; Henriksen and Dokken 2006; King et al. 2013). Therefore, inhibition of GSK-3 activity is a promising strategy in treatment of insulin resistance in obesity and type 2 diabetes. Some natural products have been found effective in the reduction of the activity of GSK-3β in cellular and diabetic animal models. For example, curcumin (**9**) strongly inhibited the activity of GSK-3β with IC_{50} value of 0.0663 μM in an in vitro assay. In vivo, it increased the liver glycogen content through suppression of GSK-3 activity in the liver (Bustanji et al. 2009b). Citrus flavonoids, luteolin (**196**),

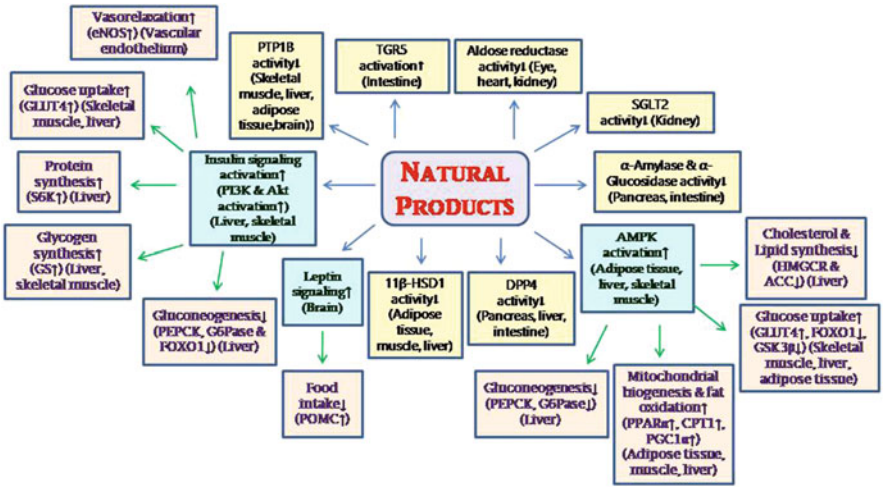

Fig. 4.3 Major therapeutic targets of natural products in diabetes treatment

apigenin (**197**), and quercetin (**23**) inhibited the activity of GSK-3β with IC_{50} of 1.5, 1.9, and 2.0 μM, respectively, in a luminescent kinase assay (Johnson et al. 2011). Accumulating evidence demonstrates that cAMP-dependent activation of PKA promotes the activity of GSK-3β in the upregulation of tyrosinase expression for melanogenesis in murine melanoma B16 cells and human melanocytes. Andrographolide (**335**), a labdane diterpenoid, from *Andrographis paniculata* decreased the melanin content and tyrosinase activity in B16F10 melanoma cells by increasing the phosphorylated level of GSK-3β and decreasing the expression of microphthalmia-associated transcription factor (MITF) in B16F10 cells (Khaled et al. 2002, 2009; Zhu et al. 2015). Polydatin (**336**), a glucoside of resveratrol, from *Polygonum cuspidatum* bark improved hyperglycemia and hyperlipidemia in diabetic rats by increasing the phosphorylation level of GSK-3β and decreasing the expression of G6Pase and SREBP-1c via insulin-dependent Akt activation in diabetic liver and HepG2 cells (Hao et al. 2014). A fraction from Chinese antidiabetic plant, *Sinocrassula indica*, inhibited the activity of GSK-3β and promoted glucose metabolism by upregulation of GLUT4 translocation in skeletal muscle of diabetic KK-Ay mice and in L6 myotubes and H411E hepatocytes via increasing the phosphorylation of GSK-3β (Yin et al. 2009). The major therapeutic targets of natural products against diabetes are presented in Fig. 4.3.

4.8 Natural Products Isolated from Various Natural Sources in Diabetes Treatment

Several natural products including the extracts from plants, dietary seaweeds, mushrooms, and various types of phytochemicals have been reported to exhibit antidiabetic activity in both cellular and animal models. These dietary natural

extracts and phytochemicals may provide a better and more efficient therapeutic approach to treat diabetes with minimal adverse effects. A few review articles highlighted the antidiabetic effect of some selected plants and phytochemicals. A list of plants, seaweeds, and mushrooms having antidiabetic efficacy and their main active components and mechanism of actions in treatment of diabetes is provided in Table 4.2.

Table 4.2 prepared on the basis of literature demonstrates that the plants belonging to 48 families, seaweeds from 5 families, and mushrooms from 8 families showed significant antidiabetic effects in cellular and animal models of diabetes. Among the plant families, the 14 families, namely, Apiaceae, Apocynaceae, Asteraceae, Cucurbitaceae, Dioscoreaceae, Fabaceae, Lamiaceae, Menispermaceae, Moraceae, Myrtaceae, Oleaceae, Oxalidaceae, Rhizophoraceae, and Rutaceae, contain large numbers of antidiabetic plants compared with other plant families. Moreover, some plants from other families, such as *Pandanus tectorius* from Pandanaceae, *Dendrobium officinale* from Orchidaceae, *Phyllanthus niruri* from Phyllanthaceae, *Plantago asiatica* from Plantaginaceae, *Nigella sativa* from Ranunculaceae, *Eriobotrya japonica* from Rosaceae, *Mimusops elengi* from Sapotaceae, and *Lycium barbarum* from Solaniaceae have potential antidiabetic effect. From these antidiabetic plants, the bioactive phytochemicals, namely, polysaccharides, flavonoids, terpenoids, alkaloids, and phenolic acids, modulate the activity of insulin via activation of AMPK and Akt in the skeletal muscle, liver, and adipose tissue for glucose uptake by upregulation of GLUT4 proteins in the skeletal muscle, liver, and adipose tissue and GLUT2 proteins in the liver and glucose utilization by glycogen synthesis by upregulation of GS enzyme activity in the liver. Moreover, insulin signaling inhibits hepatic glucose production through suppression of the expression of gluconeogenic genes, G6Pase and PEPCK. The AMPK activation in skeletal muscle, adipose tissue, and liver reduces dyslipidemia by increasing hydrolysis (lipolysis) of TG and fatty acid oxidation and decreasing the synthesis of fatty acids and cholesterol by regulation of related genes. These plant extracts and their active constituents improve insulin secretion from pancreatic β-cells and β-cell regeneration by suppression of oxidative stress, inflammation, and β-cell apoptosis through upregulation of the activity of antioxidant enzymes, SOD, CAT, and GP_X, and glucose-dependent insulin signaling pathway in pancreas. Moreover, the bioactive plant extracts/phytochemicals inhibit the activity of dietary carbohydrate digestive enzymes, α-amylase, and α-glucosidase. Some plant extracts inhibit the expression and activity of GSK-3β to promote glycogen synthesis in the liver and skeletal muscle. Various phlorotannins and polysaccharides from seaweeds, *Ecklonia cava*, *Ishige okamurae*, *Laminaria japonica*, and *Sargassum patens* reduce intestinal carbohydrates absorption by inhibition of the activity of α-amylase and α-glucosidase. Several identified and unidentified polysaccharides from mushrooms, *Agaricus bisporus*, *Cordyceps militaris*, *Ganoderma atrum*, *Hericium erinaceus*, *Grifola frondosa*, *Inonotus obliquus*, *Pleurotus pulmonarius*, and other *Pleurotus* spp., *P. florida* and *P. eryngii*, improve insulin secretion and insulin action for improvement of hyperglycemia and hyperlipidemia in diabetic animals. Possibly, these polysaccharides increase the fermentation process in gut by

gut microbiota for production of SCFAs to promote incretins secretion from intestinal L and K cells for insulin secretion from pancreas and insulin action in the metabolic tissues, liver, muscle, and adipose tissue. Fucoidans and proteins from marine animals, sea cucumbers, and terpenoids from marine sponges also exhibit potential insulin-like effect by activation of insulin signaling in diabetic rats and in in vitro assays. Therefore, these dietary plants, seaweeds, mushrooms, and marine animals could be utilized as nutraceuticals and diet supplements for treatment and prevention of diabetes.

4.9 Summary and Future Perspectives

Both obesity and its associated diabetes are complex metabolic disorders and caused by the interactions of genetic, epigenetic, dietary, lifestyle, and environmental factors. In the last three decades, the number of people with obesity and diabetes is increased rapidly in an alarming rate worldwide, about more than doubled, making these diseases as emergency health hazard to all nations. Currently, many synthetic drugs are being used for management of these diseases. Most of these drugs have harmful side effects and limit their utilization. The use of natural/herbal medicines for the treatment of various diseases has a long and extensive history. For this reason, the phytomedicines are considered to be used as a first choice of safe and low cost drugs as an alternative. Several polyherbal formulations prepared on the basis of traditional ethnobotanical and ethnopharmacological knowledge have been found potential antiobesity and antidiabetic effects. These polyherbal formulations contain various types of bioactive phytochemicals, which act in multiple targets for amelioration of these diseases. However, detail scientific knowledge on the composition and contents of phytochemicals present in them and their mode of actions is inadequate. As a result, the pharmacologists fail to prepare the formulations to get maximum efficacy from these herbal formulations. Several factors, such as cultivar effect, propagation effect, environmental factors (soil, climatic condition, geographical location, etc.), harvesting effect, postharvest storage effect, and packaging effect, are responsible for the composition and contents of the desired phytochemicals. Hence, adequate knowledge in these areas could be helpful for the farmers/growers to get maximum yields of these phytochemicals in their harvested crops. The extracts from various natural sources, namely, plants, seaweeds, mushrooms, marine animals, and microorganisms, have been reported to have potential antiobesity and antidiabetic effect. According to the literature, the plants from 59 families have been found antiobesity effect. The plant families Apiaceae, Apocynaceae, Araliaceae, Asteraceae, Celastraceae, Dioscoreaceae, Fabaceae, Lamiaceae, Solaniaceae, Theaceae, and Zingiberaceae contribute large number of plants having antiobesity efficacy and have a variety of phytochemicals. Dietary seaweeds from 12 families have significant antiobesity effect. Various sulfated polysaccharides and bromophenols from brown seaweeds/marine algae of families Alariaceae, Ishigaceae, Lessoniaceae, Laminariaceae, Sargassaceae, and Scytosiphonaceae have strong antiobesity effect. The extracts from the fruiting

bodies of edible and medicinal mushrooms from 8 families have significant antiobesity effect. Some dietary marine fishes and cucumbers have antiobesity activity. The extracts from these natural sources act through multiple targets against the pathogenesis of obesity for amelioration of the disease. The major targets are inhibition of the activity of dietary fat-digesting enzyme pancreatic lipase, suppressive effect on appetite, stimulatory effect on energy expenditure, inhibition of adipogenesis, regulation of lipid metabolism, and modulation of gut microbiota composition. These extracts from natural sources stimulate the activation of AMPK and insulin signaling pathway to increase insulin sensitivity in metabolic tissues for suppression of inflammation and synthesis of cholesterol and triglycerides and promotion of fat oxidation and mitochondrial biogenesis and glucose uptake in the liver, skeletal muscle, and adipose tissue, but deactivate AMPK in the hypothalamus in the brain to stimulate leptin signaling for suppression of food intake and in pancreas to stimulate insulin secretion. In addition, these natural polyphenols, polysaccharides and proteins increase the generation of pancreatic β-cells and secretion of insulin from β-cells by TGR5 activation as well as improve the integrity of gut barrier function for protection of the entry of harmful pathogens into systemic circulation and gut microbial activity for production of health-promoting bacteria to increase mucin synthesis, SCFAs production, and GLP-1 secretion from intestine by acting as probiotics and prebiotics.

The available literature on natural products reveal that plants belonging to 48 families, seaweeds from 5 families, and mushrooms from 8 families have been found to possess significant antidiabetic effect. Among them, the plants from families Anacardiaceae, Apiaceae, Apocynaceae, Asteraceae, Cucurbitaceae, Fabaceae, Lamiaceae, Moraceae, Myrtaceae, Oxalidaceae, Rosaceae, and Rutaceae and seaweeds from families Ishigeaceae, Lessoniaceae, and Sargassaceae, as well as mushrooms from families *Ganodermataceae*, *Hericiaceae*, *Hymenochaetaceae*, and *Pleurotaceae*, are in greater numbers compared to other families and have potential antidiabetic effect. The major bioactive phytochemicals of various classes, namely, flavonoids, anthocyanins, alkaloids, polyphenolic acids, tannins, terpenoids, saponins, organosulfur compounds, polyacetylenes, and saponins present in various bioactive natural extracts, act against the pathogenesis of diabetes through multiple targets. Their various bioactive major therapeutic targets include (a) the stimulation of AMPK activation and (b) PI3K/Akt insulin signaling pathway; (c) inhibition of the activity of dietary carbohydrate digesting enzymes α-amylase and α-glucosidase; (d) the inhibition of the activity of renal glucose reabsorption enzyme SGLT2; (e) inhibition of the the activity of DPP4 enzyme, a key enzyme responsible for deactivation of incretins that are secreted from intestinal K and L-cells; (f) inhibition of the activity of PTP1B enzyme, a negative regulator of insulin signaling pathway in peripheral tissues, and leptin signaling in hypothalamic brain; (g) inhibition of the activity of 11β-HSD1, a key regulator for induction of insulin resistance in metabolic tissues via formation of cortisol; (h) inhibition of the activity of GSK-3β, an inhibitor of the activity of the enzyme glycogen synthase (GS) in glycogen synthesis in the liver and muscle; (i) inhibition of the activity of aldose reductase (AR), a key enzyme in RAS activation and in development of diabetic vascular complications, renal

diseases, retinopathy, neuropathy, and myocardial infarction; and (j) activation of TGR5 protein, an agonist of bile acids, which on upregulation in enteroendocrine cells in intestine promotes energy expenditure in BAT to increase the expression of thermogenic genes, including UCP-1 and UCP3. These phytogenic chemicals increase glucose uptake in the liver, adipose tissue, and skeletal muscle by upregulation of GLUT4 expression; promote fat oxidation by upregulation of the expression of PPARα, CPT1, PGC-1α, and their target genes; promote lipolysis by upregulation of the expression of LPL and HSL; and suppress lipid and cholesterol synthesis by downregulation of the expression of ACC, PPARγ, C/EBPα, SREBP-1, SREBP2, FAS, HMGCR, and their target genes.

The most of the reported studies on antiobesity and antidiabetic activities of natural products isolated from various natural sources are not up to the mark for clinical trials in humans. Most of the studies are conducted in cellular and rodent models. The mutation of genes in humans and rodents is not similar and for this reason anomaly in antiobesity and antidiabetic efficacy of natural products in animal and human studies was found. These studies did not investigate the optimal doses, toxicities, and detailed pharmacokinetics of the extracts rich in phytochemicals and requisite maximum concentrations of phytochemicals to get optimum efficacy. Therefore, further research are required on the antiobesogenic and antidiabetic natural extracts and their active components to evaluate their optimum doses and long-term and short-term toxicities in animal models having mimic human genes related to obesity and diabetes. Only, a limited number of natural resources have been chemically and pharmaceutically investigated so far and hence further investigation is necessary for isolation of new drugs from unexplored plants and marine biosources.

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