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Diversity, phytochemical and medicinal potential of the genus *Ocimum* L. (*Lamiaceae*)

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Abstract *Ocimum*, commonly known as Tulsi, is a huge genus within family *Lamiaceae*, comprising about 64 species of annual to perennial aromatic medicinal herbs with a long history of traditional uses. The aromatic plants of the genus *Ocimum* have long been used as flavouring agents, as well as diverse medicinal applications. Our comprehensive review covers the published literature through the period from 1961 to April 2019 and provides a complete survey of nearly all the studied species up to date. Additionally, all related taxonomic data, geographical distribution as well as different traditional uses are discussed here in details. The major chemical classes within the genus *Ocimum* include flavonoids, phenolic acids and terpenes. The bioactivities of various extracts or individual compounds, both in vitro and in vivo, include antimicrobial, cytotoxic, antinociceptive, anti-inflammatory, antihyperglycemic and antioxidant. This comprehensive review will serve as a database for future research and drug development from the genus *Ocimum*.

Keywords *Lamiaceae* · *Ocimum* · Taxonomy · Phytoconstituents · Biological activities

Abbreviations

AAPH	2,2′-Azobis (2-amidinopropane) dihydrochloride
APCI-MS	Atmospheric pressure chemical ionization mass spectrometry
BW	Body weight
^{13}C-NMR	Carbon nuclear magnetic resonance
CC	Column chromatography
CC_{50}	Half cytotoxic concentration
DMBA	7,12-Dimethylbenzo anthracene
DPPH	2,2-Diphenyl-1-picryl-hydrazyl-hydrate
DW	Dry weight
ED_{50}	Half effective dose
EGFR	Epidermal growth factor receptor
FW	Fresh weight
Gal	Galactose
GC/MS	Gas chromatography/mass spectrometry
Glc	Glucose
GlcA	Glucouronic acid
^{1}H	Proton nuclear magnetic resonance

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HIV	Human immunodeficiency virus
HPTLC	High performance thin layer chromatography
IC_{50}	50% Inhibitory concentration
IC_{90}	90% Inhibitory concentration
LC_{50}	50% Lethal concentration
ICAP-AES	Inductively coupled argon plasma atomic spectroscopy
Ip.	Intraperitoneal
LD_{50}	50% Lethal dose
LDL	Low density lipoproteins
LIBS	Laser induced breakdown spectroscopy
LMI%	Percentage leucocyte migration inhibition
Me	Methyl
MES	Maximal electric shock
MI	Maximal inhibition
MIC	Minimum inhibitory concentration
μM	Micromolar
NF-$_K$B	Nuclear factor Kappa B
OMe	Methoxy
OSCC	Oral squamous cell carcinoma
Pg	Pico gram
PGE2	Prostaglandin E2
PhAs	Phenolic acids
RAP	Randomly amplified polymorphic DNA
Rha	Rhamnose
SAR	Structure activity relationship
UPLC–ESI–MS/MS	Ultra performance liquid chromatography
VLDL	Very low density lipoproteins
ZOI	Zone of inhibition
Xyl	Xylose

Introduction

Natural products have attracted considerable attention with their diverse pharmacological, cosmetic and food industry applications. Today, there is a growing interest towards exploring natural herbal products to solve many health care problems, via both coupling traditional knowledge with medicinal principles and obtaining the advantage of having fewer side effects. Today, many of *Lamiaceous* species are used as medicinal and aromatic plants such as *Oregano*, *Mentha*, *Rosemary* and many others. In our review, we would like to portray one genus, under the botanical name "*Ocimum*", derived from the Greek meaning "to be fragrant", and which is commonly known under the vernacular name "Tulsi" (Bhasin 2012). It is a genus of aromatic plants, belonging to the tropical tribe "*Ocimeae*", comprising about 160 species indigenous to tropical regions of Asia, Africa, Central and South America, with the main center of diversity in Africa (Simon et al. 1999). Recently, a phylogenetic study has recognized 64 species (O'Leary 2016) which are highly valued for their medicinal and aromatic properties in the traditional and modern pharmacological systems. In general, plants of *Ocimum* are herbs, under shrubs or shrubs containing essential oils of various aromas which are valuable in pharmaceutical, perfumery and food processing industry (Singh and Chaudhuri 2018). According to published literature, the specific taxonomic description of the genus *Ocimum* L. is still debatable. The genus comprises three subgenera: *Ocimum* (classified into three sections: *Ocimum*, *Gratissima* and *Hiantia*), *Nautochilus*, and *Gymnocimum* (Flegkas et al. 2019).

Among the diverse bioactive compounds of the genus *Ocimum*, terpenoids, flavonoids and phenolic acids prevailed (Fig. 1). Moreover, biological investigations have been carried out on these compounds and demonstrated their varied bioactivities such as cytotoxic, antimicrobial, and gastroprotective ones (Tan et al. 2002; Ma et al. 2005; Sharma et al. 2012). The current review focuses on recent advances in the taxonomy, phytochemistry, synthesis, biosynthesis, bioactivity and bioavailability of about 260 different compounds as well as different fractions from diverse species of *Ocimum*, with a special emphasis on *O. sanctum*, *O. basilicum* and *O. gratissimum*, the data which have been collected over the period from 1961 till April 2019. For a comprehensive literature overview, the published phytochemical and pharmacological data have been evaluated through several search engines, such as Pubmed®, Science direct®, SciFinder, ISI®, Scopus® and Google Scholar®, along with Databases such as Metlin and DNP, using '*Ocimum*' as the search keyword. We disregarded publications pertaining to agronomy, plant pathology, ecology and other unrelated topics (unless any phytochemical or pharmacological data were thoroughly available).

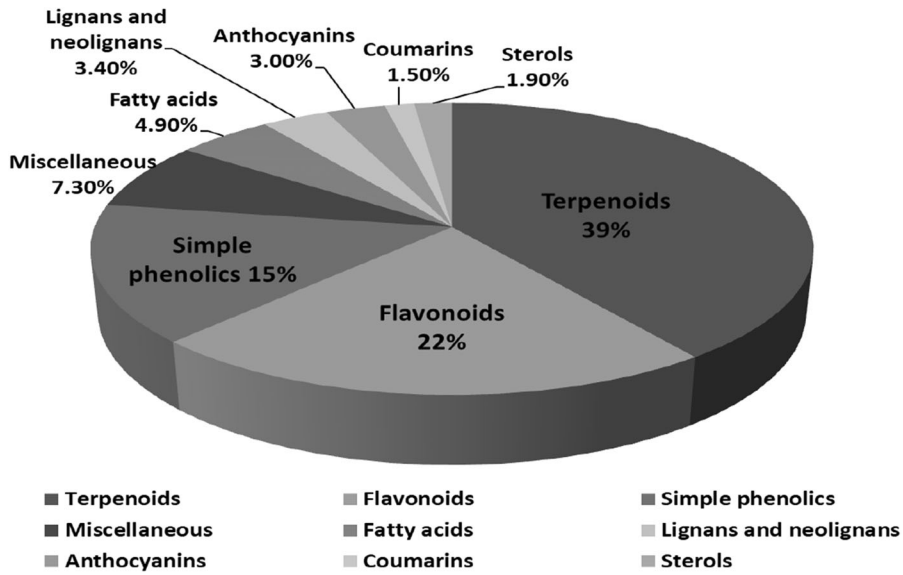


Fig. 1 Percentages of different classes of compounds distributed in the genus *Ocimum*

Taxonomic diversity

Morphological studies on *Ocimum* species showed that they reach up to 2 m or more in height with a small degree of variability in the most recorded traits including, leaf colour and shape, stem, inflorescence, flower and seed production, which further hardens the dependence on morphology for taxonomic identification. Synonyms according to http://www.theplantlist.org/ and detailed morphological features of the most well-studied species are listed in Table 1. Several aromatic compounds can be found in chemotypes of basil reflecting a great variation of available scents and flavors, where many of them contained a combination of linalool and methylchavicol and/or 1,8-cineole, reflecting the traditional sweet basil aroma (Simon et al. 1999). The cultivars showed a wide diversity in growth habit, flower, leaf and stem colors, and aromas which allowed them to be attractive ornamentals. The 'Maenglak Thai Lemon', 'Osmin Purple' and 'Red Rubin Purple' basils were the most attractive and best retained ornamental basils (Phippen and Simon 1998) due to their purple leaf color, which is attributed to the genetically unstable anthocyanins in purple basils, leading to an undesirable random green sectoring and reversion over the growing season (Simon et al. 1990).

In fact, interspecific hybridization and polyploidy usually occurs within the *Ocimum* species leading to taxonomic confusion which makes it hard to recognize the genetic relationship between many basils (Grayer et al. 1996). Moreover, taxonomy is extra complicated by the existence of chemotypes or chemical races within species that do not significantly differ in morphology (Javanmardi et al. 2002). Furthermore, chemical studies of the essential oil profiles of most species revealed some variations, that's why those species from the same genus may have different scents, which might play a major rule as key markers in their taxonomy (Chowdhury et al. 2017).

All the aforementioned facts allow the variation of marker contents within *Ocimum* species, which plays a major role in the taxonomic identification. Those marker constituents in *Ocimum* species were produced by two different pathways: phenylpropanoids by the shikimic acid pathway and regular terpenes by the mevalonic acid pathway, and the complexity in *Ocimum* essential oils resulted from differences in the dominance of these species as well as their mixed pathways, morphotypes and chemotypes. Additionally, the differences in chemical composition might also be due to a number of factors including: climatic conditions, geographical locations, seasons of collection, stages of development along with the post harvest processing before oil extraction (Javanmardi et al. 2002).

Table 1 Taxonomic significance of different *Ocimum* species

Name and synonyms	Taxonomy	References
Ocimum reclinatum S.D. Williams & M. Balkwill A.J. Paton. Synonyms: *O. sanctum* L. (the most common), *O. sanctum* var. (*angustifolium* Benth., *cubensis* Gomes and *hirsutum* Benth.)	The plant is erect, annual or perennial, herbaceous with elliptic-oblong, pubescent, brownish-green or purplish leaves. Flowers are small, purplish or crimson, pentamerous, sub-sessile, bisexual, zygomorphic and bilipped. Seeds are globose to subglobose, brown with black markings and slightly mucilaginous on wetting	Paton (1992), Bhasin (2012) and Kulkarni and Adavirao (2018)
Ocimum basilicum L. Synonyms: *O. bengalense* Poir., *O. bequaertii* De Wild, *O. basilicum* var. (*album* Benth., *anisatum* Benth., *basilicum*, *densiflorum* Benth., *difforme* Benth., *glabratum* Benth., *majus* Benth., *pilosum* (Willd.) Benth., *purpurascens* Benth., *thyrsiflorum* (L.) Benth.)	The plant is erect, under shrub with ovate leaves. Flowers are white pinkish or purplish. Seeds are dark brown to black, ellipsoid and mucilaginous	Paton (1992) and Bhasin (2012)
Ocimum gratissimum L. Synonyms: *O. gratissimum* Forssk., *O. gratissimum* subsp. *gratissimum*, *O. gratissimum* var. (*gratissimum*, *hildebrandtii* Briq., *mascarenarum* Briq., *suave* (Willd.) Hook. F., subdentatum Briq.), *O. graveolens* A. Br., *O. guatemalense* Gand., *O. guineense* Schumach. & Thonn., *O. hadiense* Forssk., *O. hanningtonii* Baker., *O. hararense* Gurkr., *O. hassleri* Briq., *O. hassleri* var. *acutatum* Briq., *O. hassleri* var. *obtusifolium* Briq., *O. heckmannianum* Gurke, *O. helianthemifolium* Hochst., *O. heptodon* P. Beauv., *O. hians* Benth., *O. hians* var. *macrocaulon* Briq., *O. hians* var. *microphyllum* Briq.)	The plant is perennial, under shrub with ovate-lanceolate green leaves. Flowers are small and pale yellow. Seeds are dark brown, rugose, sub-globose and slightly mucilaginous	Paton (1992), Prabhu et al. (2009) and Bhasin (2012)
Ocimum americanum L. Synonyms: *O. amaericanum* var. *Americanum*, *O. amaericanum* var. *Pilosum* (Willd.) A.J. Paton	The plant is an annual herb, sweet scented, pubescent, with elliptic lanceolate leaves. Flowers are white pinkish or purplish. Seeds are black, narrowly elliptic and mucilaginous	Paton (1992) and Bhasin (2012)
Ocimum canescence A.J. Paton. Synonym: *O. canum* Sims. (the most common), *O. canum* var. *integrifolium* Engl., *O. capitatum* Roth., *O. capitatum* Baker and O. *capitellatum* L. F	The plant is annual with ovate leaves. Flowers are pinkish white. Seeds are dark brown, narrowly ellipsoid and mucilaginous	Paton (1992) and Bhasin (2012)
Ocimum vihpyense A.J. Paton. Synonyms: *O. viride* Willd. (the most common), *O. villosum* Forssk., *O. virgatum* Thunb., *O. viridiflorum* Roth. and *O. viscosum* Roth	The plant is perennial, erect, much branched, under shrub with elliptic lanceolate brownish green leaves. Flowers are pale yellow. Seeds are globose, brownish and non-mucilaginous	Paton (1992) and Bhasin (2012)
Ocimum kilimandscharicum Gurke. Synonyms: *O. knyanum* Vatke, *O. knyanum* var. *astephanum* Baker. and *O. konianense* A. Chev.	The plant is perennial, under shrub with simple ovate-oblong leaves. Flowers are light purplish or white. Seeds are ovoid-oblong, black to brown and mucilaginous	Paton (1992) and Bhasin (2012)
Ocimum spicatum Deflers. Synonyms: *O. suave* Willd. (the most common), *O. stamineum* Sims., *O. staminosum* Baker., *O. stenoglossum* Briq., *O. stirbeyi* Volkens & Schweinf., *O. striatum* Hochst., *O. stuhlmannii* Gurke, *O. suave* Willd, *O. suave* var. *distantidens* Briq., *O. subserratum* B. Heyne ex Hook. f., *O. suffrutescens* Schumach., *O. sylvaticum* Thonn., *O. tashiroi* Hayata., *O. tenellum* Benth., *O. tanellum* var. *glabrellum* Briq. and *O. tenellum* var. *pilosum* Briq.	The plant is perennial, under shrub, branched, highly pubescent, with ovate to ovate lanceolate greyish green leaves. Flowers are small pinkish white. Seeds are globose, dark brown and non-mucilaginous	Paton (1992) and Bhasin (2012)

Table 1 continued

Name and synonyms	Taxonomy	References
Ocimum carnosum (Spreng) Link & Otto ex Benth. Synonyms: *O. caryophyllatum* Roxb. and *O. caryophyllinum* F. Muell.	The plant is perennial, highly branched, under shrub with simple ovate-oblanceolate, dark green leaves. Flowers are small purplish. Seeds are ellipsoid, purplish to dark brown and slightly mucilaginous	Paton (1992) and Bhasin (2012)
Ocimum forskolei Benth. *O. menthiifolium* Hochst. Ex Benth., *O. hadiense* sensu E. A., *O. staminosum* Baker., *O. stirbeyi* Schwein. & Volk., *O. kelleri* Briq., *O. piliferum* Briq., *O. falcatum* Gandoger and *O. simulans* Chiov.	The plant is a perennial woody shrub with dark green lobed ovate leaves with lanceolate lamina	Paton (1992) and Bhasin (2012)

Traditional uses, folkloric significance and pharmacological activities of most common species

Ocimum sanctum Linn.

(Commonly called Sacred Tulsi, Indigenous to India, Bhasin 2012). It is known as 'the Queen of herbs' in India, and is one of the holiest and most cherished of many healing and healthy herbs of the orient and is renowned for its religious and spiritual sanctity. The whole plant (having a pungent bitter taste) is taken orally as a nerve tonic, adaptogenic and health promotor in cancer conditions (Singh and Chaudhuri 2018). The fresh leaves have stimulant and expectorant properties, the oral infusion is recommended for malarial fever, while the juice is applied in bronchitis, pharyngitis and chest complications (Bhasin 2012). Moreover, the essential oil extracted from leaves is rich in the treasured eugenol which is far used in food flavouring industry and synthesis of vanillin (Bhasin 2012). The therapeutic oral daily dose is 2–3 g leaf powder which is greatly distant from the oral LD_{50} with a value of 4505 ± 80 mg kg^{-1} b.wt., and also from the i.p. LD_{50} with a value of 3241 ± 71 mg kg^{-1} b.wt. signifying a wide safety range. In general, it is defined by the Ayurvedic Pharmacopeia of India (1999) as an "Elixir of life" and is recommended as an adaptogen helpful for adapting to stress (Muthu et al. 2006; Nazar et al. 2008; Pattanayak et al. 2010; Prakash and Gupta 2005; Sharkar et al. 2013).

Pharmacological activities

Several studies emphasized the immunomodulatory properties of the seed oil (fixed oil) which could modulate both humoral and cell-mediated immune responses and increase antibodies production. The seed oil (3 ml kg^{-1}, i.p.) was daily administered for 6 days to rats in a trial to measure the humoral response and the results significantly gave a rise in anti-sheep red blood cells (SRBC) antibody titre (8.2 ± 0.6), in comparison with the effect when co-administered with diazepam as the control (1 mg kg^{-1}, sc) with antibody titre of 8.8 ± 0.6 (Mediratta et al. 2002). The results, gained after 3 h from injecting the inflammatory stimulus, showed an inhibition of lymphokines release which allows the inflammatory cells to diverge from the site of reaction. Accordingly, besides having a direct anti-inflammatory effect, a 3 ml kg^{-1}, i.p. dose of the oil may have a relevant effect reducing chronic inflammation by inhibiting cell-mediated immune response (Singh and Majumdar 1997).

The essential oil exhibited potent anthelmintic (Rahman et al. 2011) and antileishmanial properties (Mahajan et al. 2013).

Further studies established the strong immunity enhancing and adaptogenic properties of various extracts from the plant (Lee et al. 1985; Godhwani et al. 1988; Mahajan et al. 2013). The long-term feeding of rats with fresh leaves of tulsi (200 and 400 mg kg^{-1}) resulted in suppressing both the sperm count and motility and also reducing the weight of testes, epididymis, seminal vesicles and ventral prostate. An extra study showed a significant increase in serum testosterone levels of rabbits fed with a small amount of fresh leaves of *O. sanctum,* while FSH and LH levels were significantly reduced. These results strongly support the potential use of *O. sanctum* as an effective male contraceptive agent (Rahman et al. 2011; Mahajan et al. 2013). Two further studies

Table 2 Chemical constituents isolated from different species of the genus *Ocimum* over the period 1961–April 2019

No.	Compound	Biological activity	Source	References
Flavonoids				
1	Quercetin	Antioxidant (DPPH assay), at conc. of 200 mg kg^{-1}	*O. sanctum* leaves	Grayer et al. (2002)
			O. sanctum leaves	Joseph and Nair (2013)
2	Quercetin3-*O*-xylosyl(1‴→2″) Galactoside	N.r.	*O. sanctum* leaves	Grayer et al. (2002)
3	Quercetin-3-*O*-rutinoside (Rutin)	Antiulcer against ethanol-induced ulcer, at conc. of 200 mg kg^{-1}	*O. kilimandscharicum* leaves	Grayer et al. (2002) de Lira Mota et al. (2009)
4	Quercetin-3-*O*-β-D-glucoside	Antibacterial against *S. epidermidis* and *S. aureus* (MIC = 36 μM), Antioxidant against pBR322 damage at a conc. of 10 μM	*O. minimum* aerial parts	Grayer et al. (2002), Rigano et al. (2007) and Panat et al. (2015)
			Marrubium globosum leaves	
5	Isoquercetrin	Sedative with a dose of 10 mg kg^{-1}, i.p., antiprotozoal against *E. histolytica* and antigiardial against *G. lamblia* with IC_{50} 33.1 and 106.9 μM	*O. basilicum* whole plant	Marwat et al. (2011) and Valentová et al. (2014)
			O. sanctum leaves	Naveen et al. (2017)
6	Quercetin-3-*O*-2″-gallate	N.r.	*O. basilicum* whole plant	Marwat et al. (2011)
7	Quercetin-3-*O*-(2″-*O*-galloyl)-rutinoside	Antiulcer activity	*O. basilicum* whole plant	Marwat et al. (2011)
8	Quercetin-3-*O*-α-L-rhamnoside	N.r.	*O. basilicum* whole plant	Marwat et al. (2011)
9	Quercetin-3-*O*-β-D-galactoside	N.r.	*O. basilicum* whole plant	Marwat et al. (2011)
10	Quercetin-3-O-(6″-O-malonyl) glucoside	Antioxidant at a conc. of 10 μM	*O. minimum* aerial parts	Panat et al. (2015)
11	Luteolin (Eriodictyol)	Leishmanicidal against L. Major, $IC_{50} > 56$ μM, antituberculosis with docking score = − 7.8 with FtsZ protein of M. Tuberculosis, and cytotoxic with IC_{50} 78 ± 6 and 53 ± 4 μM against PC-3 and DU-145 cells of prostate carcinoma in mice	*O. sanctum* leaves	Nagaprashantha et al. (2011) and Vinukonda et al. (2012)
12	Isothymunin	N.r.	*O. sanctum* leaves	Singh and Chaudhuri (2018)
13	Luteolin-7-O-β-D-glucopyranoside	Antiinflammatory with IC_{50} 22.7 μM for NO and 15.0 μM for PGE2	*O. sanctum* leaves	Gupta et al. (2007)
14	Luteolin-7-O-β-D-glucouronide	Antiproliferative against MCF-7	*O. sanctum*	Flegkas et al. (2019)
			O. sanctum leaves	Tewari et al. (2012)
15	Luteolin-7-O-β-D-glucouronic acid-6″-methyl ester	N.r.	*O. sanctum* leaves	Gupta et al. (2007)
16	Orientin	Cytotoxic against colon cancer cell line, IC_{50} μM 290.3, and against PC-3, IC_{50} 50 μM, antioxidant with IC_{50} 3.5×10^{-2} mg ml^{-1}, a vasodilator on removed thoracic aortic rings from the New Zealand rabbits with IC_{50} 2.28 and 7.27 μM	*O. sanctum* aerial parts	Fu et al. (2006), Shoeb et al. (2007), Nagaprashantha et al. (2011) and Sharma et al. (2016)

Table 2 continued

No.	Compound	Biological activity	Source	References
17	Isoorientin	Cytotoxic against colon cancer and antioxidant	*O. sanctum* aerial parts	Shoeb et al. (2007)
18	Cirsiliol	Cytotoxic against colon cancer and antioxidant	*O. sanctum* and *O. kilimandscharicum* aerial parts	Grayer et al. (2001) and Shoeb et al. (2007)
19	Eupatorin	Cytotoxic against T-47D estrogen-receptor positive breast cancer cell line at a conc. of 6 μM	*O. sanctum* aerial parts	Grayer et al. (2001) and Brožič et al. (2009)
			O. basilicum leaves	Grayer et al. (2001)
20	5,6-Dihydroxy-7,3′,4′-trimethoxy flavone	N.r.	*O. sanctum* aerial parts	Grayer et al. (2001)
21	4′,5-Dihydroxy-3′,7,8-Trimethoxy-flavone	Antioxidant	*O. sanctum* leaves	Kelm et al. (2000) and Singh and Chaudhuri (2018)
22	Cirsilineol	Antioxidant, and antituberculosis, docking score with FtsZ protein = − 7.3 kcal mol^{-1}	*O. sanctum* leaves	Kelm et al. (2000) and Vinukonda et al. (2012)
			Justicia adhatoda leaves	Grayer et al. (2001)
			O. sanctum and *O. selloi*	
23	3′-Methoxy eupatorin	N.r.	*O. sanctum* aerial parts	Grayer et al. (2001)
25	5-Desmethyl-nobiletin	N.r.	*O. americanum* leaves	Vieira et al. (2003)
26	Chrysoeriol	Cytotoxic against T-47D breast cancer cell line, at a conc. 6 μM	*O. sanctum* leaves	Hiltunen and Holm (2003) and Brožič et al. (2009)
27	Kaempferol	Gastroprotective (acid/ethanol induced ulcer), dose 50 and 100 mg kg^{-1} and antiproliferative (HepG2 cells), IC_{50} = 30.92 μM	*O. basilicum* leaves	de Lira Mota et al. (2009), Marwat et al. (2011) and Wang et al. (2018)
			O. sanctum leaves	Mousavi et al. (2018)
28	Kaempferol-3-O-rutinoside	N.r.	*O. sanctum* leaves	Grayer et al. (2002)
29	Kaempferol-3-O-glucoside	N.r.	*O. sanctum* leaves	Grayer et al. (2002)
30	Kaempferol-3-O-malonyl glucoside	N.r.	*O. sanctum* leaves	Grayer et al. (2002)
31	Acacetin	Induce apoptotic cell death at concs. 50 and 100 μM	*O. sanctum* aerial parts	Grayer et al. (2001) and Singh et al. (2005)
			O. basilicum leaves	Grayer et al. (2001)
32	Apigenin 7,4′-dimethylether	N.r.	*O. sanctum* aerial parts	Grayer et al. (2001)
			O. basilicum leaves	Grayer et al. (2001)
33	Pectolinarigenin	Antiproliferative in MCF-7 breast cancer	*O. sanctum* aerial parts	Grayer et al. (2001) and Lu et al. (2014)
			Cirsium japonicum	
34	Salvigenin	Potent neuroprotective, conc. 25 μM	*O. canum* leaves	Xaasan et al. (1980) and Rafatian et al. (2012)

Table 2 continued

No.	Compound	Biological activity	Source	References
			O. basilicum, *O. minimum* and *O. selloi* leaves	Grayer et al. (2001)
35	Pilosin	N.r.	*O. sanctum* and *O. americanum* aerial parts	Grayer et al. (2001)
			O. canum leaves	Vieira et al. (2003)
36	Pedunculin	N.r.	*O. sanctum* aerial parts	Grayer et al. (2001)
37	Nevadensin	Antidiabetic, antiinflammatory, anticancer against p40 cell line with IC_{50} 112.6 μM, antibacterial and antifungal	*O. canum* seeds *Limnophila conferta*	Xaasan et al. (1980), Vieira et al. (2003) and Brahmachari (2010)
			O. basilicum and *O. minimum*	Grayer et al. (2001)
38	Gardenin B	N.r.	*O. sanctum*, *O. basilicum* and *O. minimum* aerial parts	Grayer et al. (2001)
39	Galuteolin	N.r.	*O. basilicum* leaves	Hiltunen and Holm (2003)
40	Apigenin-5-O-β-D-glucoside	N.r.	*O. sanctum* leaves	Gupta et al. (2007)
41	5-Hydroxy-6,7,8,3′,4′-pentamethoxy-flavone	N.r.	*O. sanctum* aerial parts	Grayer et al. (2001)
42	Baicalin	Cytotoxic against T-47D breast cancer cell line, conc. 6 μM	*O. sanctum* leaves	Brožič et al. (2009) and Mousavi et al. (2018)
43	Apigenin	Antioxidant, COX-1 enzyme inhibition 65%, Antituberculosis against FtsZ with docking score = − 7.6 kcal mol^{-1} and anti-alzeheimer	*O. sanctum* leaves *Justicia adhatoda*	Kelm et al. (2000), Vinukonda et al. (2012) and Singh and Chaudhuri (2018)
			O. basilicum leaves	Grayer et al. (2001)
44	Vicenin II	Antibacterial against E. coli and Proteus. Cytotoxic against LNCaP and (PC-3, DU-145) with IC_{50} 44 ± 3 and 25 ± 3 μM, respectively, and radioprotectant in Swiss albino mice (conc. 50 μg kg^{-1} i.p.)	*O. sanctum* leaves	Baruah et al. (2018), Devi et al. (1999) and Uma Devi et al. (2000)
45	Apigenin-7-O-glucouronide	N.r.	*O. sanctum* leaves	Gupta et al. (2007)
46	Apigenin-7-O-β-D-glucoside	Cytotoxic against melanoma cancer cell (B16F10), conc. 60 μM	*O. sanctum* leaves	Gupta et al. (2007) and Bouzaiene et al. (2016)
47	Genkwanin	Cytotoxic against melanoma cancer cell (B16F10), conc. 60 μM	*O. sanctum* aerial parts	Grayer et al. (2001) and Bouzaiene et al. (2016)
			O. basilicum leaves	Grayer et al. (2001)
			O. canum leaves	Vieira et al. (2003)
48	Isoscutellarein-7,8-dimethoxy flavone	Leishmanicidal against L. major with IC_{50} 25 μM	*O. sanctum* leaves	Singh and Chaudhuri (2018)
49	Molludistin	N.r.	*O. sanctum* leaves	Singh and Chaudhuri (2018)
50	Vitexin	Cytotoxic against leukemia cell line U937	*O. sanctum* leaves	He et al. (2016) and Singh and Chaudhuri (2018)

Table 2 continued

No.	Compound	Biological activity	Source	References
51	Isovitexin	Antiinflammatory, IC_{50} 17.76 ± 0.53 μM (UA is the positive control, IC_{50} of 5.99 ± 0.22 μM), and anti-alzeheimer's	*O. sanctum* leaves	Singh and Chaudhuri (2018)
52	Scutellarein	Cytotoxic against T-47D cell line, conc. 6 μM	*O. canum* leaves	Vieira et al. (2003) and Brožič et al. (2009)
53	Ladanein	Antibacterial against E-coli, Antioxidant (DPPH assay) IC_{50} 5.3 ± 0.3 μM, and cytotoxic against HT-29 and T47D cell lines	*O. sanctum* aerial parts	Grayer et al. (2001) and Farjam et al. (2013)
			Salvia sharifii leaves	
			O. basilicum leaves	Grayer et al. (2001)
54	Cirsimaritin	Antioxidant of COX-1 enzyme	*O. sanctum* leaves	Kelm et al. (2000)
			O. basilicum leaves	Grayer et al. (2001)
55	Hispidulin	Antiviral with neuraminidase activity, IC_{50} 19.83 ± 2.28 μM, EC_{50} 22.62 ± 1.79 μM and CC_{50} > 200 μM	*O. canum* leaves	Bang et al. (2016) and Singh and Chaudhuri (2018)
			Salvia plebeia	
			O. basilicum leaves	Grayer et al. (2001)
56	Isothymusin	N.r.	*O. grandiflorum* and *O. gratissimum* leaves	Grayer et al. (2001)
57	Xanthomicrol	Vasodilator, decrease tone and contraction of rat ileum	*O. sanctum* and *O. americanum* aerial parts	Grayer et al. (2001)
58	Isosakuranetin	N.r.	*O. sanctum* leaves	Mousavi et al. (2018)
Lignans				
59	(–) rabdosiin	Cytotoxic against MCF-7, SKBR3, and HCT-116 cell lines	*O. basilicum* leaves	Flegkas et al. (2019)
60	Shimobashiric acid A	Cytotoxic against MCF-7 cell line	*O. basilicum* leaves	Flegkas et al. (2019)
Neolignans				
61–67	Tulsinols A–G	Leishmanicidal against L. major, the most significant is Tulsinol C, IC_{50} 20.5 μM	*O. sanctum* leaves	Suzuki et al. (2009)
Phenolic acids and phenyl propanoids				
68	Syringic acid	Antibacterial, against E. coli and P. mirabilis	*O. sanctum* aerial parts	Mondal et al. (2009) and Alves et al. (2013)
			Wild mushrooms	
69	Gallic acid	Antibacterial, against E. coli and P. mirabilis	*O. sanctum* aerial parts	Mondal et al. (2009) and Alves et al. (2013)
			Wild mushrooms	
70	Gallic acid methyl ester	Antibacterial against 10 strains of S. aureus with MIC range from 7.3 to 28 μM	*O. sanctum* aerial parts	Mondal et al. (2009) and Al-Zahrani (2012)
71	Gallic acid ethyl ester	N.r.	*O. sanctum* aerial parts	Mondal et al. (2009)
72	Protocatechuic acid	Antibacterial against lactobacillus spp., E. coli and bacillus spp.	*O. sanctum* aerial parts	Mondal et al. (2009) and Sánchez-Maldonado et al. (2011)

Table 2 continued

No.	Compound	Biological activity	Source	References
73	Methyl salicylate	N.r.	*O. sanctum* aerial parts	Mondal et al. (2009)
74	Vanillic acid	Antibacterial, against E. coli and P. mirabilis	*O. sanctum* aerial parts	Skaltsa et al. (1999) and Alves et al. (2013)
			Wild mushrooms	
75	Vanillin	Anticancer against A549 lung cancer, 4T1 mammary adenocarcinoma, and HepG2 carcinoma	*O. sanctum* aerial parts	Mondal et al. (2009) and Zhu et al. (2017)
			Curcumin	
76	4-Hydroxybenzoic acid	Antibacterial against lactobacillus spp., E. coli and bacillus spp	*O. sanctum* aerial parts	Mondal et al. (2009) and Sánchez-Maldonado et al. (2011)
77	4-Hydroxy-benzaldehyde	N.r.	*O. sanctum* aerial parts	Mondal et al. (2009)
78	Phenylpropene 4-Allyl-1-O-glucosyl-2-hydroxybenzene	N.r.	*O. sanctum* leaves	Suzuki et al. (2009)
79	4-Allyl-1-O-glucosyl-2-methoxybenzene	N.r.	*O. sanctum* leaves	Suzuki et al. (2009)
80	Estragol (methyl chavicol)	Antioxidant, antimicrobial, antiinflammatory and anxiolytic	*O. selloi* essential oil	de Paula et al. (2003) and Silva-Alves et al. (2013)
			O. sanctum and *O. basilicum* essential oil	Vani et al. (2009)
81	Ociglycoside	N.r.	*O. sanctum* leaves	Suzuki et al. (2009)
82	Citrusin C	Superoxide scavenging (4.3%) and tyrosinase inhibitory (47.2 and 87.9%) activities at conc. 1.5 μM, compared with Arbutin as a control with 0.8 μM and (7.7 and 63% inhibition)	*O. sanctum* leaves	Sawabe et al. (2005) and Suzuki et al. (2009)
			Hibiscus subdariffa	
83	Eugenol	Leishmanicidal against L. major, antimicrobial against E. coli and M. luteus, antioxidant (COX-1 inhibition and DPPH assay), nematicidal against nematode infection of H. esculentus, conc. 0.2 ml L^{-1}	*O. sanctum* leaves	Kelm et al. (2000), Sacchetti et al. (2004), Politeo et al. (2007) and Suzuki et al. (2009)
			O. sanctum and *O. basilicum* essential oil	Vani et al. (2009)
84	Methyl eugenol	Antimicrobial against Micrococcus flavus and antifungal against Aspergillus niger	*O. micranthum* aerial parts	Sacchetti et al. (2004) and Joshi (2013)
			O. sanctum and *O. basilicum* essential oil	Vani et al. (2009)
85	3-(3,4-Dihydroxy-phenyl)-2-hydroxypropanoic acid	Antiproliferative against MCF-7.	*O. basilicum* leaves	Flegkas et al. (2019)
86	Lithospermic acid	Antioxidant inhibit formation of superoxide radicals at IC_{50} 2.43 μM	*O. basilicum* roots	Tada et al. (1996)

Table 2 continued

No.	Compound	Biological activity	Source	References
87	Caftaric acid	Antihepatotoxic against amphetamine-induced toxicity at a dose of 40 mg kg^{-1}	*O. basilicum* leaves	Marwat et al. (2011) and Koriem and Soliman (2014)
88	3,4,5-Trimethoxy cinnamic acid	Anti-proliferative, antitumour, antimicrobial, estrogenic and anti-inflammatory	*O. sanctum* leaves	Mousavi et al. (2018)
89	Ocimum naphthanoic acid	N.r.	*O. sanctum* leaves	Ali and Ali (2012)
90	Chlorogenic acid	Anticolon cancer, antioxidant and antibacterial properties	*O. basilicum* leaves	Shoeb et al. (2007)
91	P-Coumaric acid	Antibacterial against Lactobacillus spp., E. coli and bacillus spp		Sánchez-Maldonado et al. (2011)
92	(E)-P-coumaroyl-4-O-β-D-glucoside	Antiproliferative against MCF-7	*O. basilicum* leaves	Flegkas et al. (2019)
93	Ferulic acid	Antibacterial against Lactobacillus spp., E. coli and bacillus spp.	*O. kilimandscharicum*	Sánchez-Maldonado et al. (2011)
94	Caffeic acid	Antibacterial against Lactobacillus spp., E. coli and bacillus spp.	*O. kilimandscharicum*	Sánchez-Maldonado et al. (2011)
			O. sanctum leaves	Singh and Chaudhuri (2018)
			O. sanctum leaves	Mousavi et al. (2018)
95	Sinapic acid	Cytotoxicity in V79 and HeLa cell lines.	*O. kilimandscharicum*	Sánchez-Maldonado et al. (2011)
96	Methyl-cinnamate	N.r.	*O. kilimandscharicum*	Sánchez-Maldonado et al. (2011)
97	Syringin	Apoptotic at conc. 5 and 20 μM with about 0.98 ± 0.02 and 0.90 ± 0.01 folds suppression, respectively.	*O. basilicum* whole plant	Marwat et al. (2011) and US et al. (2015)
98	Ferulaldehyde	Significant antileishmanial with IC_{50} 2.27 μM	*O. sanctum* leaves	Suzuki et al. (2009)
99	Chicoric acid	Antiviral, against HIV-1 integrase	*O. basilicum* leaves *Salvia plebeia*	Lee and Scagel (2009) and Bang et al. (2016)
100	Rosmarinic acid	Antioxidant (COX-1 enzyme inhibition), antimicrobial against Pseudomonas aeruginosa, Antituberculosis, docking score = − 7.9 with FtsZ protein of M. tuberculosis	*O. basilicum* roots *Justicia adhatoda*	Tada et al. (1996), Kelm et al. (2000) and Vinukonda et al. (2012)
101	Rosmarinic acid methyl ester	Antiviral against (H1N1) with neuraminidase inhibitory activity, IC_{50} 16.65 ± 0.19 μM, EC_{50} 22.6 ± 2.76 μM, CC_{50} ~ 200 μM	*O. basilicum* root	Tada et al. (1996), Bang et al. (2016) and Singh and Chaudhuri (2018)
102	1″-Menthyl-2-glucopyranosyl-oxybenzoate	N.r.		
103	Bieugenol	Leishmanicidal against L. major, IC_{50} 30.6 μM	*O. sanctum* leaves	Suzuki et al. (2009)
104	Dehydrodieugenol B	Leishmanicidal against L. major, IC_{50} 37.3 μM	*O. sanctum* leaves	Suzuki et al. (2009)
105	Trans anethol	Mosquitorepellent activity, conc. 10% v/v	*O. selloi*	de Paula et al. (2003)
106	Cis anethol	Mosquitorepellent activity, conc. 10% v/v	*O. selloi*	de Paula et al. (2003)

Table 2 continued

No.	Compound	Biological activity	Source	References
107	Myristicin	Insecticidal against larvae of Spilarctia obliqua, with LD_{50} 104 µg/larva, dose (200 µg g^{-1} diet) in diet mix, 100% mortality	*O. basilicum* leaves *Piper mullesua*	Lee et al. (2007) and Marwat et al. (2011)
Anthocyanins				
108	Cyanidin	Gastroprotective against: (Pylorus ligation, dose 12.5 mg kg^{-1}), (stress, dose 100.0 mg kg^{-1}) (Phenylbutazone, dose 22.0 mg kg^{-1}), (Indomethacin, 100.0 mg kg^{-1}), (Reserpine, 100 mg kg^{-1}), (Ethanol, 24.9 mg kg^{-1}), (Cysteamine, 50.0 mg kg^{-1})	*O. basilicum* leaves	Phippen and Simon (1998) and de Lira Mota et al. (2009)
109	Cyanidine-3,5-diglucoside	N.r.	*O. basilicum* leaves	Phippen and Simon (1998)
110	Peonidin	N.r.	*O. basilicum* leaves	Phippen and Simon (1998)
111	Peonidin-3,5-diglucoside	N.r.	*O. basilicum* leaves	Phippen and Simon (1998)
112	Cyanidine-3-glucoside	Apoptotic on HS578T Cells at a conc. of 10 µM	*O. basilicum* leaves	Phippen and Simon (1998) and Chen et al. (2005)
113	Cyanidin-3-(p-coumaryl glucoside)	N.r.	*O. basilicum* leaves	Phippen and Simon (1998)
114	Cyanidin 3-(p-coumaryl glucoside)-5-glucoside	N.r.	*O. basilicum* leaves	Phippen and Simon (1998)
115	Peonidin 3-(p-coumaryl glucoside)-5-glucoside	N.r.	*O. basilicum* leaves	Phippen and Simon (1998)
Coumarins				
116	Coumarin	Antifungal against C. albicans, the SC5314 strain	*O. basilicum* whole plant	Marwat et al. (2011) and Jia et al. (2018)
117	Aesculetin	Antioxidant (DPPH assay), IC_{50} 4.7 µM, anti apoptosis against U937 cells	*O. basilicum* whole plant *Fraxinus chinensis*	Chu et al. (2001) and Marwat et al. (2011)
			O. sanctum leaves	Singh and Chaudhuri (2018)
118	Aesculin	Antioxidant (DPPH assay).	*O. basilicum* whole plant	Chu et al. (2001) and Lee et al. (2007)
			O. sanctum leaves	Singh and Chaudhuri (2018)
119	Ocimarin	Antituberculosis, docking score = − 7.3 with FtsZ protein of M. tuberculosis	*O. basilicum* whole plant *O. sanctum* leaves	Singh and Chaudhuri (2018)
Triterpenes				
120	Ursolic acid	Cytotoxic against HL-60, BGC, Bel-7402 and Hela, cell lines Antioxidant, antinociceptive, antihyperglycemic, antihyperlipidemic, antituberculosis with docking score of FtsZ protein = − 7.8 kcal mol^{-1}	*O. sanctum* leaves *O. amaericanum*, *O. selloi* and *O. gratissimum*	Hiltunen and Holm (2003), Ma et al. (2005), Senthil et al. (2007) and Suzuki et al. (2009) Silva et al. (2008)

Table 2 continued

No.	Compound	Biological activity	Source	References
121	Urs-12-en-3B,6B,20B-triol-28-oic acid	N.r.		Singh and Chaudhuri (2018)
122	3-Epimaslinic acid	Hepatoprotective activity	*O. basilicum* roots	Marzouk (2009)
123	Pomolic acid	Increased the total of apoptotic cells by 42% at 100 μM and by 71% at 200 μM	*O. basilicum* roots and seeds *Cecropia pachystachya*	Schinella et al. (2008) and Marwat et al. (2011)
124	Oleanolic acid	Leishmanicidal against L. major, IC_{50} 38.5 μM, and cytotoxic, and antituberculosis, ith docking score = − 7.3 with FtsZ protein of M. tuberculosis	*O. canum* leaves and flowers	Prabhu et al. (2009) and Suzuki et al. (2009)
			O. sanctum leaves	Vinukonda et al. (2012) Mahajan et al. (2013)
125	Alphitolic acid	Antibacterial against Gm +ve bacteria, and hepatpprotective against CCl4 induced oxidative stress	*O. basilicum* seeds and fruits *Zizyphus joazeiro*	Marzouk (2009) and Schühly et al. (1999)
126	Betulin	Cytotoxic and antiproliferative	*O. basilicum* seeds and roots	Marwat et al. (2011) and Zhao et al. (2018)
127	Betulinic acid	Antibacterial against Gm +ve bacteria	*O. basilicum* seeds and roots	Marzouk (2009)
128	Euscaphoic acid	Hepatoprotective activity	*O. basilicum* roots	Marzouk (2009)
129	Basilol	N.r.	*O. basilicum* aerial parts	Siddiqui et al. (2007)
130	Ocimol	N.r.	*O. basilicum* aerial parts	Siddiqui et al. (2007)
Monoterpene hydrocarbons (no reportd activity for the single compounds)				
131	3-Carene		*O. basilicum*	Hiltunen and Holm (2003)
132	p-Cymene		*O. gratissimum*	Prabhu et al. (2009)
			O. canum	Sanda et al. (1998)
133	Limonene		*O. kilimandscharicum* leaves	Narwal et al. (2011)
134	Myrcene		*O. forskolei*	Fatope et al. (2008)
			O. canum	Sanda et al. (1998)
135	β-Ocimene		*O. basilicum*	Hiltunen and Holm (2003)
			O. basilicum essential oil	Vani et al. (2009)
			O. forskolei essential oil	Fatope et al. (2008)
136	Allo-ocimene		*O. basilicum*	Hussain et al. (2008)
137	α-Phellanderene		*O. basilicum*	Hussain et al. (2008)
			O. kilimandscharicum leaves	Narwal et al. (2011)
138	β-Phellandrene		*O. basilicum*	Hiltunen and Holm (2003)
139	α-Pinene		*O. forskolei*	Al-Hajj et al. (2014)
			O. kilimandscharicum leaves	Narwal et al. (2011)

Table 2 continued

No.	Compound	Biological activity	Source	References
140	β-Pinene		*O. forskolei*	Prabhu et al. (2009)
141	Sabinene		*O. basilicum*	Prabhu et al. (2009)
			O. sanctum essential oil	Vani et al. (2009)
142	α-Terpinene		*O. basilicum*	Fatope et al. (2008)
			O. kilimandscharicum leaves	Narwal et al. (2011)
143	β-Terpinene		*O. basilicum*	Hiltunen and Holm (2003)
144	Terpinolene		*O. basilicum*	Hussain et al. (2008)
145	α-Thujene		*O. basilicum*	Hiltunen and Holm (2003)
Oxugenated monoterpenes				
146	Borneol	Positive modulators of GABA action at human recombinant a1b2g2L GABAA receptors	*O. basilicum*	Hiltunen and Holm (2003)
			O. sanctum and *O. basilicum* essential oil	Vani et al. (2009)
147	Bornyl acetate	Positive modulators of GABA action at human recombinant a1b2g2L GABAA receptors	*O. rubrum*	Granger et al. (2005) and Karawya et al. (1974)
148	Camphor	Positive modulators of GABA action at human recombinant a1b2g2L GABAA receptors, mosquito repellent	*O. basilicum*	Hussain et al. (2008), Granger et al. (2005) and Fu et al. (2015)
			Cinnamonum camphora	
			O. canum	Sanda et al. (1998)
149	1,8-Cineole	Mosquito-repellent activity at a dose of 10 µl kg^{-1} against S. granarius and S. zeamais	*O. basilicum*	Hussain et al. (2008) and Bayala et al. (2014)
			O. forskolei essential oil	Fatope et al. (2008)
150	Citronellal	Antibacterial against Brevibacterium casei with zone of inhibition 9 mm	*O. rubrum* essential oil	Karawya et al. (1974) and Kotan et al. (2007)
			O. basilicum and *O. americanum*	Carović-Stanko et al. (2010)
151	Citronellol	Antibacterial against Kocuria varians with zone of inhibition 9 mm	*O. rubrum*	Karawya et al. (1974) and Kotan et al. (2007)
			O. basilicum and *O. americanum*	Carović-Stanko et al. (2010)
152	Citronellyl acetate	N.r.	*O. basilicum*	Hussain et al. (2008)
153	Fenchone	N.r.	*O. rubrum*	Karawya et al. (1974)
			O. gratissimum leaves	Prabhu et al. (2009)
154	Fenchyl acetate	N.r.	*O. basilicum*	Hussain et al. (2008)
155	Fenchyl alcohol	N.r.	*O. basilicum*	Hussain et al. (2008)
156	Geranial	N.r.	*O. urticifolia*	Chagonda et al. (2000)
157	Geraniol	N.r.	*O. forskolei*	Fatope et al. (2008)
			O. basilicum and *O. americanum*	Carović-Stanko et al. (2010)
158	Geranyl acetate	Antibacterial against Xanthomonas campestris pv. Campestris with zone of inhibition 7 mm	*O. basilicum*	Kotan et al. (2007) and Hussain et al. (2008)
			O. americanum	Carović-Stanko et al. (2010)

Table 2 continued

No.	Compound	Biological activity	Source	References
159	Isobornyl acetate	N.r.	*O. micranthum*	Sacchetti et al. (2004)
160	Linalool	Antigiardial against Giardia lamblia	*O. basilicum*	de Almeida et al. (2007)
			O. kilimandscharicum leaves	Prabhu et al. (2009)
161	Linalool oxide	Antinociceptive, anticonvulsive, dose 150 mg kg^{-1} reduced duration of tonic seizures in the MES test, and increased latency to first seizure in the PTZ test	*O. urticifolia*	Chagonda et al. (2000) and Souto-Maior et al. (2017)
			O. basilicum essential oil	Fatope et al. (2008)
162	Linalyl acetate	Antibacterial against Erwinia carotovora	*O. basilicum*	Kotan et al. (2007) and Hussain et al. (2008)
163	Menthol	Antibacterial against Kocuria varians	*O. basilicum*	Kotan et al. (2007) and Hussain et al. (2008)
164	Menthone	Antibacterial against Clavibacter michiganense	*O. basilicum*	Hussain et al. (2008)
165	Myrtenal	N.r.	*O. urticifolia*	Chagonda et al. (2000)
166	Neral	N.r.	*O. urticifolia*	Chagonda et al. (2000)
			O. basilicum and *O. americanum*	Carović-Stanko et al. (2010)
167	Nerol	Antibacterial against Brevibacillus brevis	*O. urticifolia*	Chagonda et al. (2000) and Kotan et al. (2007)
			O. basilicum essential oil	Politeo et al. (2007)
168	Neryl acetate	Antibacterial against Brevibacterium casei	*O. basilicum*	Hussain et al. (2008)
169	Trans-ocimene oxide	N.r.	*O. urticifolia*	Chagonda et al. (2000)
170	Perilla aldehyde	N.r.	*O. basilicum*	Hussain et al. (2008)
171	Terpinen-4-ol	Antibacterial against Clavibacter michiganense	*O. basilicum*	Kotan et al. (2007) and Hussain et al. (2008)
172	α-Terpineol	Antibacterial against Clavibacter michiganense	*O. basilicum*	Hussain et al. (2008)
			O. americanum essential oil	Carović-Stanko et al. (2010)
173	α-Terpinyl acetate	N.r.	*O. basilicum*	Hussain et al. (2008)
174	Thujone	N.r.	*O. basilicum*	Hussain et al. (2008)
			O. canum	Sanda et al. (1998)
			O. americanum	Carović-Stanko et al. (2010)
175	Sabinene hydrate	N.r.	*O. basilicum*	Hussain et al. (2008)
			O. americanum essential oil	Carović-Stanko et al. (2010)
Sesquiterpene hydrocarbons				
176	α-Amorphene	N.r.	*O. kilimandscharicum*	Ntezurubanza et al. (1984)
			O. sanctum essential oil	
177	Cis-α-bergamotene	Antioxidant and antiinflammatory	*O. kilimandscharicum*	Ntezurubanza et al. (1984) and Bayala et al. (2014)
			O. basilicum and *O. americanum*	Carović-Stanko et al. (2010)

Table 2 continued

No.	Compound	Biological activity	Source	References
178	Cis-β-bergamotene	N.r.	*O. kilimandscharicum*	Ntezurubanza et al. (1984)
179	Bicyclo-germacrene	N.r.	*O. micranthum*	Sacchetti et al. (2004)
			O. sanctum essential oil	Vani et al. (2009)
180	Bicycloelemene	N.r.	*O. kilimandscharicum*	Ntezurubanza et al. (1984)
			O. basilicum and *O. americanum*	Carović-Stanko et al. (2010)
181	α-Bisabolene	N.r.	*O. kilimandscharicum*	Ntezurubanza et al. (1984)
182	β-Bisabolene	N.r.	*O. kilimandscharicum*	Ntezurubanza et al. (1984)
			O. basilicum and *O. americanum*	Carović-Stanko et al. (2010)
183	Bourbonene	N.r.	*O. urticifolia*	Ntezurubanza et al. (1984)
184	α-Cadinene	Leishmanicidal against L. major with IC_{50} 9 μM and IC_{90} 15.7 μM	*O. micranthum*	Sacchetti et al. (2004)
			O. basilicum essential oil	Vani et al. (2009)
185	Calamenene	N.r.	*O. kilimandscharicum*	Ntezurubanza et al. (1984)
186	β-Caryophyllene	Antiproliferative activity against MCF-7 cell line, IC_{50} values 15.7 μM	*O. kilimandscharicum*	Ntezurubanza et al. (1984) and Singh et al. (2014)
			O. gratissimum leaves	Prabhu et al. (2009)
			O. sanctum leaves	Prabhu et al. (2009)
187	α-Caryophyllene	N.r.	*O. sanctum*	Kothari et al. (2004)
			O. gratissimum leaves	Prabhu et al. (2009)
188	β-Cedrene	N.r.	*O. micranthum*	Sacchetti et al. (2004)
189	α-Copaene	N.r.	*O. forskolei*	Dekker et al. (2011)
190	β-Copaene	N.r.	*O. micranthum*	Charles et al. (1990)
191	α-Cubebene	N.r.	*O. micranthum*	Sacchetti et al. (2004)
			O. basilicum essential oil	Vani et al. (2009)
192	Cyclosativene	N.r.	*O. sanctum*	Singh and Chaudhuri (2018)
193	β-Elemene	N.r.	*O. sanctum*	Machado et al. (1999)
			O. basilicum essential oil	Vani et al. (2009)
194	α-Elemene	N.r.	*O. sanctum*	Machado et al. (1999)
195	α-Farnesene	N.r.	*O. sanctum*	Singh and Chaudhuri (2018)
			O. canum	Sanda et al. (1998)
196	Germacrene-D	N.r.	*O. canum*	Martins et al. (1999)
			O. basilicum essential oil	Vani et al. (2009)
197	Germacrene-B	N.r.	*O. sanctum*	Machado et al. (1999)
			O. forskolei essential oil	Fatope et al. (2008)
198	α-Guaiene	N.r.	*O. sanctum*	Singh and Chaudhuri (2018)
199	β-Gurjunene	N.r.	*O. sanctum*	Singh and Chaudhuri (2018)
200	α-Humulene	N.r.	*O. forskolei*	Fatope et al. (2008)
			O. basilicum essential oil	Vani et al. (2009)
201	Isocaryo-phyllen	N.r.	*O. sanctum*	Singh and Chaudhuri (2018)
202	Ledene	N.r.	*O. sanctum*	Singh and Chaudhuri (2018)
203	β-Patchoulene	N.r.	*O. sanctum*	Singh and Chaudhuri (2018)
204	α-Santalene	N.r.	*O. sanctum*	Singh and Chaudhuri (2018)
205	α-Selinene	N.r.	*O. urticifolia*	Chagonda et al. (2000)

Table 2 continued

No.	Compound	Biological activity	Source	References
206	β-Selinene	N.r.	*O. urticifolia*	Chagonda et al. (2000)
			O. basilicum and *O. americanum*	Carović-Stanko et al. (2010)
207	B-Sesquiphell-andrene	N.r.	*O. kilimandscharicum*	Ntezurubanza et al. (1984)
208	B-Caryophyllene oxide	Antiproliferative activity against MCF-7 cell line with IC_{50} values of 10.8 μM	*O. sanctum*	Machado et al. (1999) and Singh et al. (2014)
			O. forskolei essential oil	Fatope et al. (2008)
209	2(Hydroxymeth-yl)-5,5,9–trimethyl cyclo [7.2.0.0.3,6] undecan-2-ol	Antiproliferative against MCF-7 cell line (MTT assay), IC_{50} values of 30 ± 0.5 μM	*O. sanctum*	Singh et al. (2014)
Oxygenated sesquiterpenes (No reportd activity for the single compounds)				
210	α-Bisabolol		All are from *O. basilicum* leaves	Hiltunen and Holm (2003)
211	β-Bisabolol			
212	Bulnesol			
213	Trans cadinol			
214	β-Eudesmol			
215	Farnesol			
216	Nerolidol			
217	Ledol			
218	Spathulenol			
219	Calamenene			
Others (No reportd activity for the single compounds)				
220	P-Methoxy acetophenone		All are from *O. basilicum*	Hiltunen and Holm (2003) and Hussain et al. (2008)
221	β-Damascenone			
222	2,4-Decadienal			
223	Decanol			
224	Dodecanol			
225	Cuminaldehyde			
226	Methyl jasmonate			
227	Methyl epijasmonate			
228	Cis-jasmonate			
229	3-Octanol			
230	2,4-Octadienal			
231	3-Octanone			
232	Octanol			
233	1-Octen-3-ol			
234	Octyl acetate			
235	2-Methyl-3-methoxy pyrazine			
236	Quinoline			
237	Undecylaldehyde			
238	Methyl jasmonate			

Table 2 continued

No.	Compound	Biological activity	Source	References
Fatty acids (all from fixed oil of seeds)				
239	Oleic acid	Antimicrobial, conc. 56 μM, mean % inhibition 27.33, 0, 73.00, 57.1, and 100% (S. mutans, A. actinomycetes, P. gingivalis, C. albicans and S. gordonii, respectively)	*O. sanctum* *O. basilicum*	Mondal et al. (2009) Nour et al. (2009)
240	Linoleic acid	Antimicrobial, conc. 56 μM, mean % inhibition 100, 88.5, 38.3, 96.81 and 100% (S. mutans, A. Actinomycetes, P. gingivalis, C. Albicans and S. gordonii, respectively)	*O. sanctum* *O. basilicum*	Mondal et al. (2009) Nour et al. (2009)
241	Linolenic acid	Antibacterial against Pneumococci with MIC 0.4 μM	*O. sanctum* *O. basilicum*	Kabara et al. (1972) and Mondal et al. (2009) Nour et al. (2009)
242	Stearic acid	N.r.	*O. sanctum* *O. basilicum*	Mondal et al. (2009) Nour et al. (2009)
243	Palmitic acid	Antibacterial against Pneumococci with MIC 0.48 μM.	*O. sanctum* *O. basilicum*	Kabara et al. (1972) and Mondal et al. (2009) Nour et al. (2009)
244	Ocimumoside A (Cerebroside)	Antistress, significant ($\rho < 0.05$) at conc. 40 mg kg^{-1} by normalizing hyperglycemia, plasma corticosterone, plasma creatine kinase and adrenal hypertrophy in Sprague-Dawley rats	*O. sanctum*	Gupta et al. (2007)
245	Ocimumoside B (Cerebroside)	Antistress, significant ($\rho < 0.05$) at conc. 40 mg kg^{-1} by normalizing plasma corticosterone, plasma creatine kinase and adrenal hypertrophy in Sprague-Dawley rats	*O. sanctum*	Gupta et al. (2007)
246	Sanctumoic acid	N.r.	*O. sanctum*	Ali and Ali (2012)
247	Capryl tetraglycosidic salicylate	N.r.	*O. sanctum*	Ali and Ali (2012)
248	Oleyl glucoside	N.r.	*O. sanctum*	Ali and Ali (2012)
249	Diglucosyloleate	N.r.	*O. sanctum*	Ali and Ali (2012)
250	Benzoyl gluco-oleate	N.r.	*O. sanctum*	Ali and Ali (2012)
251	1,3-Dilinoleneoyl-2-palmitin	N.r.	*O. sanctum*	Singh and Chaudhuri (2018)
Sterols				
252	β-Sitosterol	Antidiabetic (against streptozotocin induced diabetes), anti oxidant, and cytotoxic against prostate cancer cells decreasing cell growth by 24%, at conc. of 16 μM	*O. basilicum* *O. sanctum* leaves	Hiltunen and Holm (2003), Gupta et al. (2011) and Saeidnia et al. (2014) Singh and Chaudhuri (2018)
253	Daucosterol	Antifungal against C. albicans and C. tropicalis, MIC, 56 μM (control: fluconazol, MIC, 11.26 μM). antimicrobial activities against S. aureus, methicillin-resistant S. aureus, P. mirabilis, S. typhi, K. pneumonia and E. coli	*O. sanctum* leaves	Rahmana et al. (2009), Njinga et al. (2016) and Saeidnia et al. (2014)

Table 2 continued

No.	Compound	Biological activity	Source	References
254	Stigmasterol	Leishmanicidal against L. major and antituberculosis, docking score with FtsZ protein − 8.6 kcal mol^{-1}	*O. sanctum* leaves	Suzuki et al. (2009) and Vinukonda et al. (2012)
255	Basilimoside	N.r.	*O. basilicum* aerial parts	Siddiqui et al. (2007)
256	Campesterol	N.r.	*O. basilicum* leaves	Tewari et al. (2012)
Polysaccharides				
257	Rhamnose		*O. basilicum* seeds	Anjaneyalu and Gowda (1979)
258	Xylose			
259	Glucose			
260	Galacturonic acid			

reported the anti-tuberculosis potential of crude extract of fresh leaves against respiratory disorders (Kelm et al. 2000; Vinukonda et al. 2012), while a third study evaluated the antitussive and antimalarial efficiencies of the ethanol extract, which reinforced its folkloric use as an expectorant, antitussive and against chest problems (Inbaneson et al. 2012).

The designed extract named OciBest (developped by M/s Natural Remedies Pvt. Ltd., Bangalore, India) is obtained by blending water with methanol extract of the whole plant, following the required level of active constituents from ociglycoside-I (> 0.1% w/w), rosmarinic acid (> 0.2% w/w), oleanolic acid and ursolic acid (> 2.5%). This extract proved efficacy against chronic variable stress disorders (Chandrasekaran et al. 2013).

**Ocimum basilicum* L.

(Commonly known as Rehan, sweet Basil and is native to India, Bhasin 2012). Indian basils have edible leaves of which their decoction is used as a stimulant, expectorant and as a demulcent for throat congestions, besides proving efficacy against asthma, inflammation and enlarged spleen cases (Mathews et al. 1993).

Pharmacological activities

The i.p. administration of essential oil doses, higher than 0.2 ml kg^{-1} in mice, significantly impaired the CNS motor activity and increased the latency of convulsions and percent of animals exhibiting clonic seizures. The ED_{50} values of the essential oil were 0.61, 0.43 and 1.27 ml kg^{-1}, when tested against pentylenetetrazole, picrotoxin, and strychnine-induced convulsions in mice, respectively (Zheljazkov et al. 2007a).

Both alcoholic and aqueous extracts of the whole plant of *O. basilicum* exhibited a stimulant cardiotonic and adrenergic effect on frog heart with significant positive ionotropic and negative chronotropic actions ($P < 0.05$) which were antagonized by propranolol (Bilal et al. 2012). In addition, a good hepatoprotective activity was obtained by ethanolic extract of leaves of *Ocimum basilicum* against liver damage induced by H_2O_2 (Bilal et al. 2012).

**Ocimum gratissimum* L.

(Commonly known as Ram Tulsi, Indigenous to India, Bhasin 2012). The essential oil yield is 0.21% with eugenol as the major component 67% (Nakamura et al. 1999). The ethanolic extract of leaves is orally used in traditional medicine for treatment of urinary tract and GI infections (Bhasin 2012). Whereas, the essential oil is pale yellow in colour, with a high percentage of eugenol, and it is employed in flavouring food products, beverages, dental preparations, topical antiseptics and for usage in the treatment of minor wounds, boils and pimples as well as repelling mosquitoes (Bhasin 2012).

Pharmacological activities

The essential oil obtained from leaves showed significant antibacterial potency against *Staphylococcus aureus* at MIC of 0.75 μg ml^{-1} and against *Shigella*, *Salmonella* and *E. coli* at MIC 3–12 μg ml^{-1}. Moderate anthelmintic (Pessoa et al. 2002), antileishmanial (Ueda-Nakamura et al. 2006) and antimalarial (Tchoumbougnang et al. 2005) activities of the oil have been stated. The methanolic extract of the plant exhibited a hypoglycemic activity (Aguiyi et al. 2000) while the alcoholic leaf extract showed an antidiarrhoeal one (Ilori et al. 1996).

**Ocimum americanum* L.

(Commonly called Kali Tulsi, Indigenous to India, Bhasin 2012). A decoction of leaves is orally taken for cough, dysentery, bronchitis, immunity disturbance and as a mouth wash for reliving toothache (Chopra et al. 1958). Besides, the essential oil, with citral as the main constituent, is pale yellow in colour with a characteristic odour of lemon, which is externally used in perfumes and pharmaceutical industry.

Pharmacological activities

Many studies proved the anti-inflammatory and antioxidant potential of the essential oil of *O. gratissimum* (Bayala et al. 2014) as well as the mosquito repellent (Bayala et al. 2014), antimicrobial (Thaweboon and Thaweboon 2009) and larvicidal properties (Cavalcanti et al. 2004).

**Ocimum canum* Sims.

(Commonly named as Dulal Tulsi, Indigenous to India). The whole plant infusion is orally administered to relieve fever, dysentry and nose haemorrage. Generally, the most common folkloric uses were directed towards alleviation of migrain and fever by the oral intake of leaves and seeds decoction (Chopra and Nayar 1956). Essential oil, light yellow in colour and rich with Linalool, is externally used in perfumes, flavour and cosmetic industry (Bhasin 2012).

Pharmacological activities

The essential oil was evaluated against *Giardia* and different parasites and showed strong antigiardial and antiparasitic activities (de Almeida et al. 2007) which in turn strongly supported its anti oxidant, cytotoxic and antiproliferative activities (Manosroi et al. 2006; Selvi et al. 2015). Studies have reported the antidiabetic activity (Mahajan et al. 2013) as well as the CNS sedation (Freire et al. 2006) and antiplasmodial activities of the aqueous extract (Simonsen et al. 2001).

**Ocimum viride* Willd.

(Commonly named as Van Tulsi and is native to West Africa, Bhasin 2012). A decoction of leaves is orally taken to relieve fever and cough, the fresh juice of leaves is topically applied for catarrh and as eye drops for conjunctivitis, and the poultice is externally used against rheumatism and lumbago (Bhasin 2012; CSIR 1948). The essential oil is pale yellow and viscid, with a characteristic odour of thymol and has a pungent flavor. It is extensively used in flavoring, perfumes manufacturing and in preservative purposes (Bhasin 2012).

Pharmacological activities

Studies reported the anti-inflammatory, apoptotic and cytotoxic activities of the essential oil (Sharma et al. 2010) as well as the antibacterial potential of the ethanolic extract (Pesewu et al. 2008).

**Ocimum kilimandscharicum* Guerk.

(Commonly named as Kapur Tulsi, indigenous to West Africa, Bhasin 2012). The whole plant infusion has stimulant, antifungal and antibacterial properties. Essential oil is light yellow with strong odour of camphor, and it is widely used in perfumes, flavouring, pharmaceutical purposes and in various dental and oral preparations (Khosla and Bhasin 2000; Bhasin 2012). The most common traditional use is to repel insect, which was supported by studies.

Pharmacological activities

A study proved that leaves crude extract is effective via inhalation against many types of insects (Jembere et al. 1995). Another study supported the use of that extract as a stimulant with an antiproliferative activity against MCF-7 cell line (Ntezurubanza et al. 1984).

**Ocimum suave* Willd.

(Commonly named as Wild Basil, indigenous to West Africa, Bhasin 2012). The oral administration of whole plant decoction is ethnomedicinally used for the treatment of cough, inflammation, abdominal pain and topically against ear and eye inflammation (Bhasin 2012). Regarding the essential oil, it is highly viscid with a light yellow colour and a balsamic woody dust odour. It is a rich source of sesquiterpene alcohols and it is widely used in flavouring of tobacco and snuff, as a body perfume and a mosquito repellent (Chopra et al. 1958).

Pharmacological activities

Tan et al. (2002) proved that the methanolic extract of leaves exhibited a gastroprotective effect.

**Ocimum carnosum.*

(Commonly named as Basil Pepper, indigenous to West Africa, Bhasin 2012). The fresh leaves have been traditionally used for flavouring and its odour is useful in insect repellent purposes in Brazil (Bhasin 2012). Essential oil is light yellow, viscid with strong spicy earthy odour and is a rich source of elemicin which is highly valued for its vast pharmaceutical and flavouring properties. Elemicin is widely employed in the production of 3,4,5-trimethoxy-benzaldehyde which forms the starting material for the synthesis of trimethoprim as an important antibacterial agent. The most common traditional use of the plant was to repel insects (Bhasin 2012).

Pharmacological activities

The essential oil demonstrated a strong insect repellent activity (de Paula et al. 2003).

**Ocimum forskolei* Benth.

(Commonly named as Habak and is indiginous to South Asia especially Yemen, Dekker et al. 2011). The whole plant is traditionally used as a cosmetic, antioxidant, anti-infectious and as a mosquito repellent, but the most common use is for flavouring (Waka et al. 2006; Dekker et al. 2011). Essential oil is light yellow with a high content of camphor and the oral administration of leaves extract is reported to be efficient against bacteria and dermatophytes, the results which supported its antibacterial and anti-infectious traditional uses (Al-Hajj et al. 2014; Ali et al. 2017).

Pharmacological activities

The essential oil exhibited antimicrobial, antioxidant, cytotoxic (Ali et al. 2017) and mosquito repellent activities (Dekker et al. 2011).

Out of the aforementioned collected results, the main geographical origin appears to be South Asia followed by central and west Africa, the temperate regions which may support the rule of high temperature in the production and biosynthesis of phytoconstituents. In conclusion, the main medicinal and traditional uses appeared to be concerned with immunostimulant, antimicrobial and antiinflammatory cases, as well as insect repellent purposes.

Clinical studies

Despite the long history of traditional uses of Tulsi (clinical studies usually use the term ‘Tulsi’ to refer to *O. sanctum* or *O. gratissimum*), relatively few human intervention studies have been conducted on its effectiveness against clinical conditions. The 24 human studies recognized up to date could be classified according to three main clinical domains including: metabolic disorders (15 studies), neurocognitive and mood conditions (4 studies), and immunity as well as microbial or viral infections (5 studies), all of which are extremely relevant to the growing world-wide epidemic of lifestyle-related chronic diseases (Jamshidi and Cohen 2017). Results of these studies focused on the effective adaptogenic rule of Tulsi to fight the psychological, physiological, immunological, and metabolic stress of modern living. In a further

12-week randomized trial in diabetics, 2 g of Tulsi leaf extract, whether alone or combined with neem leaf extract, produced marked reduction in diabetic symptoms with the advantage of improved efficacy as a result of the combination (Kochhar et al. 2009).

Two further clinical trials studied the effect of 10 g day^{-1} of an aqueous extract of fresh Tulsi leaves in acute viral infection patients as well as a study on patients with acute viral encephalitis could prove increased survival rates after 4 weeks in the Tulsi group compared to the dexamethasone control group which reported symptomatic improvement after 2 weeks (Das et al. 1983; Rajalakshmi et al. 1986). Moreover, a clinical trial has demonstrated an improvement in cognitive flexibility, short-term memory and attention in 40 healthy young adults (17–30 years) following daily treatment with 300 mg of tulsi for 4 weeks (Sampath et al. 2015). All reviewed studies reported favourable clinical effects with minimized or no side effects, except only one clinical trial which reported transient mild nausea (Satapathy et al. 2017). As the longest study was only 13 weeks, the failure to report any adverse effects does not preclude the presence of any long term side effects. However, the long traditional history of regular Tulsi use suggests that daily ingestion of Tulsi is safe especially against mode and immunity problems (Saxena et al. 2012).

Safety of *Ocimum*

*Ocimum sanctum

Acute toxicity studies performed on mice have used the leaves ethanol extract of *O. sanctum* and revealed that it did not harvest any hazardous symptoms, CNS and ANS toxicities or death when administered up to 2000 mg kg^{-1}. Moreover, subacute treatment did not show any changes in body weight, food or water consumption and hematological and biochemical profiles when administered up to 800 mg kg^{-1} day^{-1} for 28 days (Gautam and Goel 2014).

Furthermore, the essential oil proved safety in the "in vitro" test on primary cultures of cardiomyocytes at 1200 µg mL^{-1}, and "in vivo" when the acute oral toxicity at 2000 mg kg^{-1} was tested. Additionally, the essential oil of *Ocimum sanctum* L. var. *cubensis* showed no acute dermal toxicity on mice classifying this test substance as a "NON TOXIC" according to Directive No. 402 of the Organization for Economic Cooperation and Development (OECD). Consequently, the obtained results revealed that the oil could be considered safe, both topically and orally, without showing any in vitro or in vivo toxicity (LD_{50} of 42.5 ml kg^{-1} in rats). Accordingly, all the above-mentioned results could prove that both the ethanol *extract* and essential oil of *O. sanctum* could be safe for human use (Chil Núñez et al. 2017).

*Ocimum basilicum

The results of the acute toxicity study performed on rats showed the LD_{50} of *O. basilicum* to be higher than 5 mg kg^{-1}, while the subchronic study showed no adverse effects on serum parameters in both male and female rats. The hematological results showed a reduction in the hematocrit, platelets and RBC in both sexes, but no abnormalities were observed in other parameters. The overall results indicated that the hematologic system could serve as a target organ in oral toxicity of this plant (Rasekh et al. 2012).

*Ocimum gratissimum

In spite of its promising clinical relevance, its ingestion has been related with nephrotoxicity and hepatotoxicity following high doses of exposure (which is dose dependent (Onaolapo and Onaolapo 2012) and male reproductive toxicities (Njan et al. 2019). However, these toxicity studies focused on the crude extract and essential oils from the *Ocimum gratissimum* leaves and there have been no documented studies that investigated the probable safety of fractions from the crude leaf extract (Njan et al. 2019).

In conclusion, *O. gratissimum* may be useful in the treatment of certain ailments, but caution should be considered during the therapeutic applications of the plant (Ebeye et al. 2014).

In general, the majority of clinical trials showed minimized or no hazardous side effects, except only one which reported transient mild nausea So, *Ocimum* species can be considered safe adaptogenic herbs used to improve mode and immunity, but further standardization and wide-ranged quality control analysis are needed (Satapathy et al. 2017).

Phytoconstituents and pharmacological activities

Different classes of compounds detected in different *Ocimum* species include: flavonoids, simple phenolics, terpenoids, coumarins, anthocyanins, essential oils, fixed oils and steroids. They are summarized in Figs. 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11, and their summarized pharmacological activities are listed in Table 2.

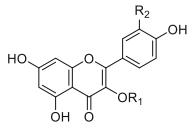
Flavonoids

So far, the literature survey has indicated the isolation of 58 flavonoids (from 1 to 58) from the genus *Ocimum*, most of them were purified from *O. sanctum* (Singh and Chaudhuri 2018).

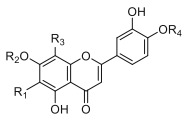
A chemical study described the distribution and natural abundance of 8-oxygenated flavones on *Ocimum* leaf surface by the aid of APCI-MS has identified six compounds: Eupatorin 19, Cirsilineol 22, Salvigenin 34, Gardenin B 38, Apigenin 43 and Cirsimaritin 54 as majors, Luteolin-7-*O*-β-D-glucopyranoside 13, Luteolin-7-*O*-β-D-glucouronide 14, Luteolin-7-*O*-β-D-glucouronic acid-6″-methyl ester 15, Apigenin-7-*O*-glucouronide 45 and Apigenin-7-*O*-β-D-glucoside 46 as common ones and Galuteolin 39 and Apigenin-5-*O*-β-D-glucoside 40 as key markers for the genus (Grayer et al. 2002). Both Quercetin 1 and its derivative, Quercetin-3-*O*-rutinoside 3 which were isolated in 2002 from *O. sanctum* and *O. kilimandscharicum* leaves, respectively, showed a strong gastroprotective effect (Table 2). The latter has a strong antibacterial activity against *S. epidermidis* and *E. faecalis* (MIC = 18 μM), when compared to tetracyclin as a positive control (MIC 0.22 and 4.5 μM, respectively) (Rigano et al. 2007). The mechanism of antibacterial action of both compounds resulted mainly from the presence of an *O*-dihydroxy in the B ring (catechol), and additionally a 2,3 double bond in conjugation with a 4-Oxo function, as well as the presence of hydroxyl groups in positions 3, 5 and 7 in their structures (de Lira Mota et al. 2009). An analogue of Quercetin 1, is Isoquercetrin 5, with an acceptable oral daily intake of 5.4 mg kg^{-1} day^{-1}, and an oral LD_{50} in Sprague-Dawley rats of > 25 g kg^{-1}, showed a high degree of safety (Valentová et al. 2014). It also displayed a significant anti-asthmatic potency, in comparison with cromolyn sodium as a control, against the ovalbumin antigenic and leukotriene-induced response in guinea pigs airways at 10 mg kg^{-1} dose and with MIC value of 6.4 μM (Marwat et al. 2011).

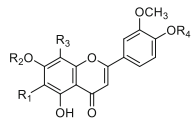
Luteolin 11 (with oral LD_{50} of 411 mg kg^{-1} in rats), a flavone isolated from *O. sanctum* leaves (Nagaprashantha et al. 2011), exhibited a significant antiviral neuraminidase activity against neuraminidase (NA) of the H1N1 influenza virus where it gave IC_{50} value of 17.96 ± 2.38 μM when compared to oseltamivir as a controI with IC_{50} value of 0.10 ± 0.02 μM. This SAR study revealed that the presence of a hydroxyl group at both C-4′ and C-7 of flavone skeleton showed greater inhibitory activity than other flavonoids lacking hydroxyl groups at the same positions (Bang et al. 2016). Other flavonoids as Orientin 16, (with i.p. LD_{50} in mice of 6.5 mg kg^{-1}) showed excellent antioxidant properties compared to dimethylsulfoxide as a control, and inhibited TBARS formation at concentrations above 0.25 μM, with % inhibition of 5.2 ± 3.13% (Uma Devi et al. 2000). It also displayed a pain relieving activity in mice with an MI of 70.3 at 10 mg kg^{-1} dose, and surprisingly, it was 20-fold more potent than acetylsalicylic acid (MI 90.1 ± 2.5 at 60 mg kg^{-1}), and 3.5-fold more dynamic than indomethacin (MI 70.6 ± 2.0 at 60 mg kg^{-1}) which gave a chance to be used as an alternative antinociceptive remedy (Da Silva et al. 2010). Salvigenin 34 displayed a strong neuroprotective potential at a concentration of 25 μM, significantly unlike chloroquine-treated cells as a standard, with verification that it acts via promoting cell servival by both inhibiting apoptosis and enhancing autophagy (Rafatian et al. 2012).

Regarding the unusual flavonoids in the *Lamiaceae*, the rare one, Nevadensin 37, is considered to be a promising natural bioactive substance (a novel natural lead) having a wide array of bioactivities (Brahmachari 2010). It unveiled an excellent activity against the H-37Rv strain of *Mycobacterium tuberculosis*, on L-J medium, at MIC 0.00022 μM (compared to streptomycin as a standard at conc. 22.5 μM) (Reddy et al. 1991). Additionally, it showed a 100% cytotoxicity at a concentration of 0.00016 μM in both Dalton's lymphoma and Ehrlich ascites tumour in another related study (Reddy et al. 1991). Concerning the significant antioxidants, Vicenin 44, is a good one which could inhibit the TBARS formation at concentrations above 0.25 μM compared to DMSO as a control which gave a % inhibition of 2.3 ± 0.26. The

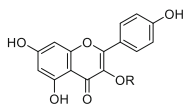


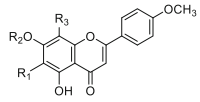
No.	R1	R2	No.	R1	R2
1	H	OH	6	β-d-glucoside-2"-gallate	OH
2	Xyl(1‴ _ 2'')Gal	OH	7	-(2"-O-galloyl)-rutinoside	OH
3	Rha(1‴ _ 6'')Glc	OH	8	α-l-rhamnoside	OH
4	β-d-Glc	OH	9	β-d-Gal	OH
5	β-d-glucofuranoside	OH	10	(6″-O-malonyl) Glc	OH

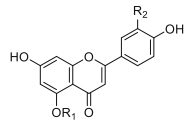




No.	R1	R2	R3	R4	No.	R1	R2	R3	R4
11	H	H	H	H	20	OH	Me	H	Me
12	OMe	Me	OH	Me	21	H	Me	OMe	H
13	H	β -d-glc	H	H	22	OMe	Me	H	H
14	H	glcA	H	H	23	OMe	Me	H	Me
15	H	β -d-glcA-6"-meth ester	H	H	24	OMe	H	OMe	Me
					25	OMe	Me	OMe	Me
16	H	H	C-glc	H	26	H	GlcA	H	H
17	β -d-glc	H	H	H					
18	OMe	Me	H	H					
19	OMe	Me	H	Me					



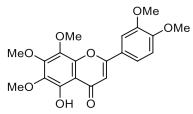




No.	R1
27	H
28	Rha(1‴ _ 6")Glc
29	Glc
30	O-(malonyl)Glc

No.	R1	R2	R3
31	H	H	H
32	H	Me	H
33	OMe	H	H
34	OMe	Me	H
35	OMe	H	OH
36	OMe	Me	OH
37	OMe	H	OMe
38	OMe	Me	OMe

No.	R1	R2
39	β -d-glc	OH
40	β -d-glc	H



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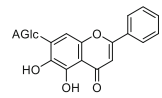
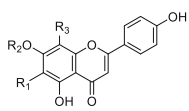
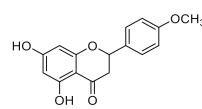


42

No.	R1	R2	R3
43	H	H	H
44	C-Glc	H	C-Glc
45	H	β-d-glcA	H
46	H	β-d-glc	H
47	H	Me	H
48	H	Me	OMe
49	H	Me	C-Xyl
50	H	H	C-Glc
51	C-Glc	H	H
52	OH	H	H

No.	R1	R2	R3
53	OH	Me	H
54	OMe	Me	H
55	OMe	H	H
56	OMe	Me	OH
57	OMe	Me	OMe





58

Fig. 2 Chemical structures of flavonoids

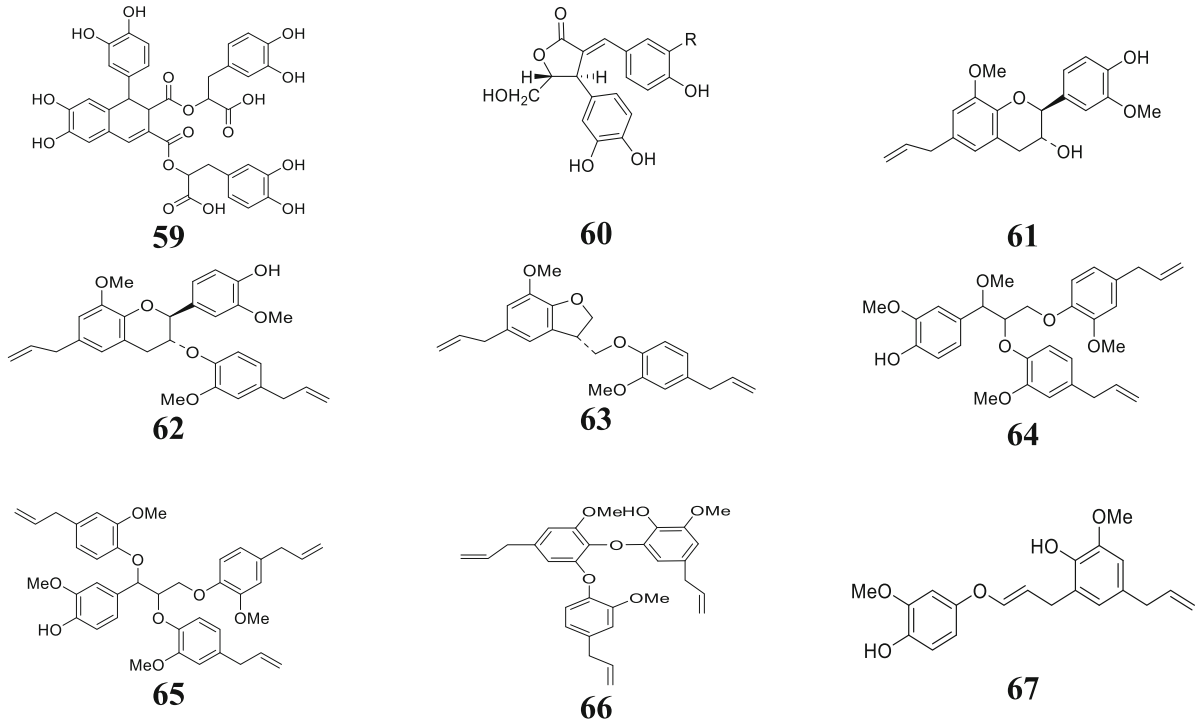


Fig. 3 Chemical structures of lignans and neolignans

mechanism of action of both Vicenin and Orientin suggested a liver protection against lipid peroxidation by scavenging the radiation-induced free radicals, thus preventing their interaction with membrane lipids (Uma Devi et al. 2000). In a recent study, the same compound, Vicenin 44 exhibited potent radiosensitizer and cytotoxic activities in non-small cell lung cancer cells, only in combination with radiation and in a dose dependent manner. The bioactive concentration of 20–50 μM of this compound caused no decrease in cell survival, the one from 60 to 100 μM caused a gradual decrease while that at a 80 μM conc. resulted in a 50.08 ± 0.048% decrease (Baruah et al. 2018).

Amongst different bioactive flavonoids isolated from the genus, was Isovitexin 51, which displayed a highly significant ($P < 0.001$) antidiabetic potential. The mechanism of antidiabetic action was suggested to be via inhibition of both RLAR and HRAR, giving IC_{50} values of 0.49 ± 0.08 and 0.13 ± 0.03 μM, in comparison with quercetin with IC_{50} values of 0.83 ± 0.10 and 0.07 ± 0.03, respectively (Moumbock et al. 2017). On the other hand, Isothymusin 56, Luteolin 11 and Apigenin 43 with oral LD_{50} 1.37 mg kg^{-1} in rats exhibited moderate anticancer activities. Anticancer molecular docking analysis illustrated their inhibitory interaction of the EGFR (one of the highly expressed proteins inducing metastasis in OSCC) and showed high gliding scores of − 9.98, − 9.51, and − 9.45 kcal mol^{-1} and binding energies of − 42.63, − 48.28, and − 44.95 kcal mol^{-1}, respectively (Moumbock et al. 2017).

Biosynthesis

The biosynthetic pathway of the synthesis of salvigenin 34 via hydroxylation and methylation of apigenin 43 (the general precursor for the pathway) occurs in the peltate trichomes on basil leaf surface. The accumulating intermediates, Apigenin 7,4′-dimethylether 32, Salvigenin 34, Genkwanin 47, Ladanein 53 and Cirsimaritin 54 as well as the key compound Apigenin 43, in connection with substrate affinities of 7-*O*, 6-*O* and 4′-*O*-methyltransferases directs the order of the metabolite decoration with methyl and hydroxyl groups and indicates the most

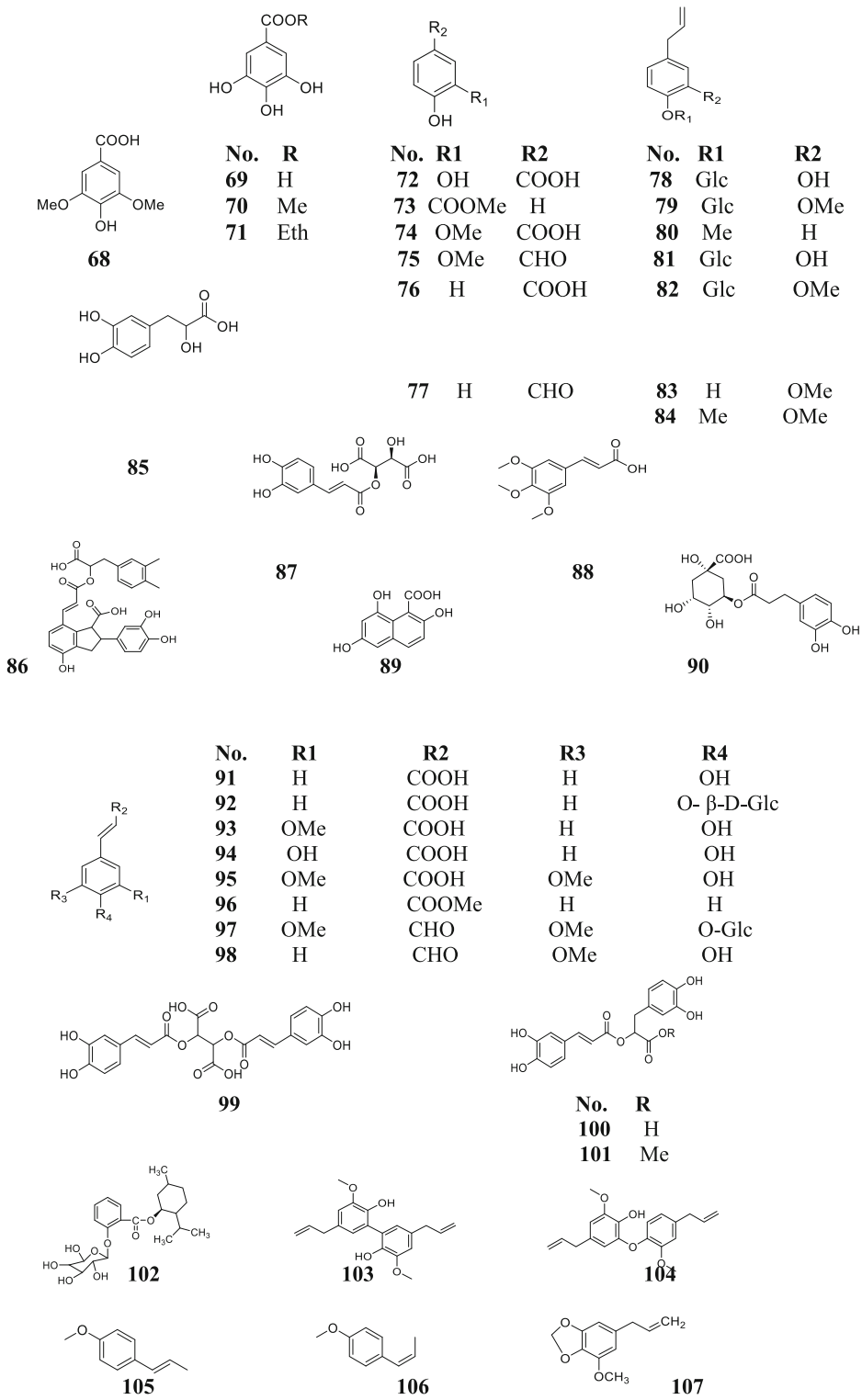
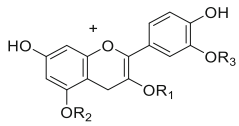


Fig. 4 Chemical structures of phenolic compounds



No.	R1	R	R3
108	H	H	H
109	Glc	Glc	H
110	H	H	Me
111	Glc	Glc	Me
112	Glc	H	H
113	P-coumaryl glc	H	H
114	P-coumaryl glc	Glc	H
115	P-coumaryl glc	Glc	Me

Fig. 5 Chemical structures of anthocyanins

favourable biosynthetic way (Berim et al. 2012). Apigenin 43 is also considered as a general precursor for the production of nevadensin 37 with a step of *O*-demethylation at the 7 position on the ring A of Gardenin B 38 as an intermediate (Berim and Gang 2013).

Bioavailability

The highest bioavailability has been recorded for isoflavones, followed by flavanols, flavanones and flavonol glycosides, while the least one was observed with proanthocyanidins, flavanol gallates and anthocyanins. Flavonoid glycosides are deglycosylated prior to the intestinal uptake, whereas aglycones are being transported to the liver to undergo extensive metabolism producing different conjugates which in turn are proposed to be responsible for the health-promoting effects of flavonoids (Viskupicova et al. 2008; Thilakarathna and Rupasinghe 2013). For example, the bioavailability of quercetin metabolites were five times higher when given to healthy human volunteers (Hollman 2004) as Quercetin-4′-*O*-glucoside (C_{max}: 2.1 ± 1.6 μg ml^{-1}) instead of Quercetin-3-*O*-rutinoside (C_{max}: 0.3 ± 0.3 μg ml^{-1}) which indicate the great effect of the type and position of sugar moiety on rate of absorption (Thilakarathna and Rupasinghe 2013).

Lignans and neolignans

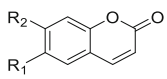
Chemical investigation of the genus *Ocimum* resulted in the isolation of 2 lignans and 7 neolignans from 59 to 67 (Table 2; Fig. 3). Lignans and neolignans are polyphenolic compounds rarely detected in *Ocimum*, but known for their leishmanicidal properties (Suzuki et al. 2009). Tulsinol A 61 and Tulsinol B 62 have very interesting structures comparable to the flavonoidal skeleton and were suggested to be synthesized from eugenol through oligomerization. Thus, they might belong to the neolignan group in a biosynthetic standpoint, and to the flavone group in a structural standpoint via having a flavan-3-ol skeleton (Suzuki et al. 2009).

Biosynthesis

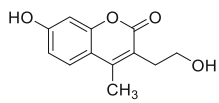
Lignans share a common biosynthetic pathway, consisting of two propyl-benzene units coupled by a β,β′-bond, thus being classified under diphenolic compounds (Rodríguez-García et al. 2019).

Bioavailability

Lignans metabolized after ingestion, by intestinal bacteria, followed by transformation to mammalian lignans (enterolactones and enterodiols) prior to absorption, which considerably decreases the risk of different types of cancer, particularly of the colon, prostate and breast (Rodríguez-García et al. 2019). Among the 9 lignans and neolignans detected in various species of *Ocimum*, Tulsinol C showed the highly significant leishmanicidal activity with IC_{50}

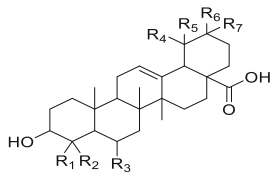


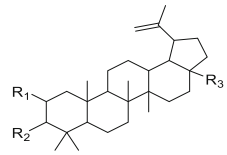
No.	R1	R2
116	H	H
117	OH	OH
118	O-Glc	OH



119

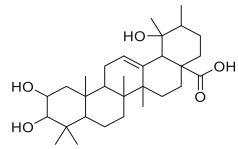
Fig. 6 Chemical structures of coumarins





No.	R1	R2	R3	R4	R5	R6	R7
120	Me	Me	H	H	Me	H	Me
121	Me	Me	OH	Me	H	Me	OH
122	Me	CH_2OH	H	OH	Me	H	Me
123	Me	Me	H	OH	Me	H	Me
124	Me	Me	H	H	H	Me	Me

	R1	R2	R3
125	OH	OH	COOH
126	H	OH	CH2OH
127	H	OH	COOH



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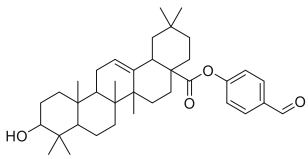

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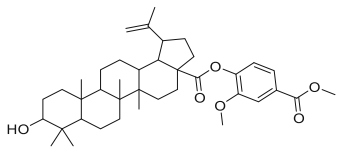

130

Fig. 7 Chemical structures of terpenoids

value of 20.5 μM ($P < 0.001$), followed by both Tulsinols A & F ($P < 0.05$), while the others were considered weakly active (Suzuki et al. 2009). On the other hand, Rabdosiin and shimobashiric acid were bioactive compounds having a diversity of moderate efficacies, but were considered as weakly active antiproliferative agents (Flegkas et al. 2019).

Phenolic compounds

Chemical investigation of *ocimum* resulted in the identification of 41 phenolic compounds over the period from 1974 to 2019 (68–107, Table 2) (Fig. 4)

Quantitative analysis of phenolic acids (PhAs) in both flower and leaf tissues gave a value of 99.62 mg g^{-1} DW, which may be due to dry and warm conditions of the geographical origin and which is protective for the plants against the fluctuating environmental conditions. Accordingly, the production of caffeic acid is highly dependent on climatic conditions. In the same context, the highest amounts of lithospermic acid 86 were observed in the flowers (2500 mg g^{-1} DW), where Syringic 68, Protocatechuic 72, Vanillic 74, *p*-coumaric 91 and Ferulic acids 93, in most of the accessions ranged around 10–250 mg g^{-1} DW and were significantly correlated with Rosmarinic acid (RA). Caffeic acid 94 concentration was the lowest in the flower and leaf extracts (< 10 mg g^{-1} DW) (Javanmardi et al. 2002). In general, since phenolics are stress-related compounds produced under harsh environmental conditions, it seems that in humid and semihumid conditions there is no need to produce these compounds (Javanmardi et al. 2002).

Considering different bioactivities of PhAs, Feruladehyde 98 exhibited a highly significant leishmanicidal activity against *Leishmania major* with IC_{50} 2.27 μM, compared to amphotericin B as a standard with IC_{50} 0.09 μM (Suzuki et al. 2009). Moreover, Chicoric acid 99, displayed a moderate but selective inhibitory activity of HIV-1 integrase at conc. 50 μM, with IC_{50} 0.1–0.5 μM for the end-processing/strand transfer reactions and 0.1–0.2 μM for the disintegration reactions, respectively (ED_{50} 1–2 μM and CT > 200 μM), compared to Oseltamivir as a control with $IC_{50} = 0.10 \pm 0.02$ μM (Bang et al. 2016).

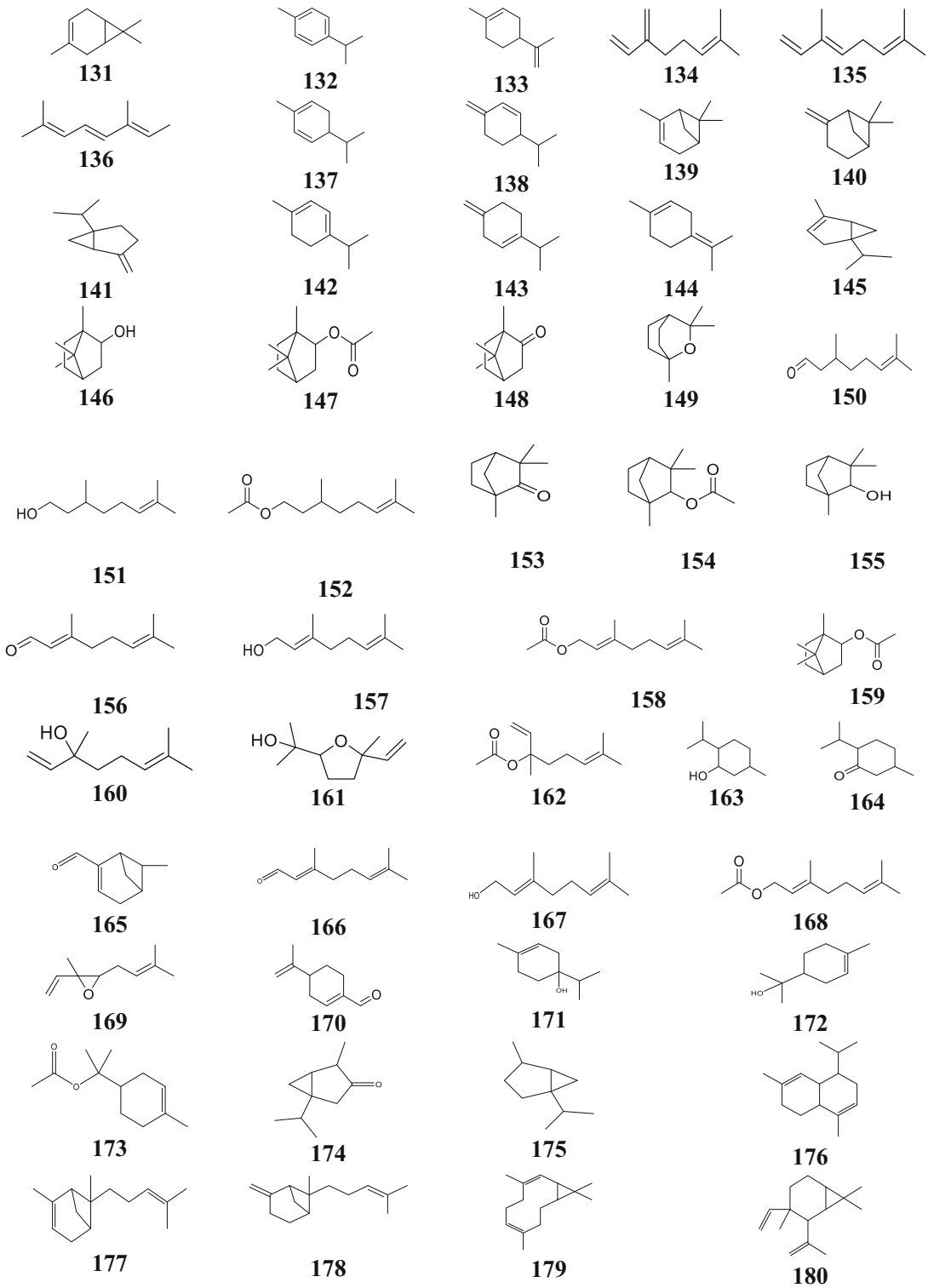

Fig. 8 Chemical structures of essential oils

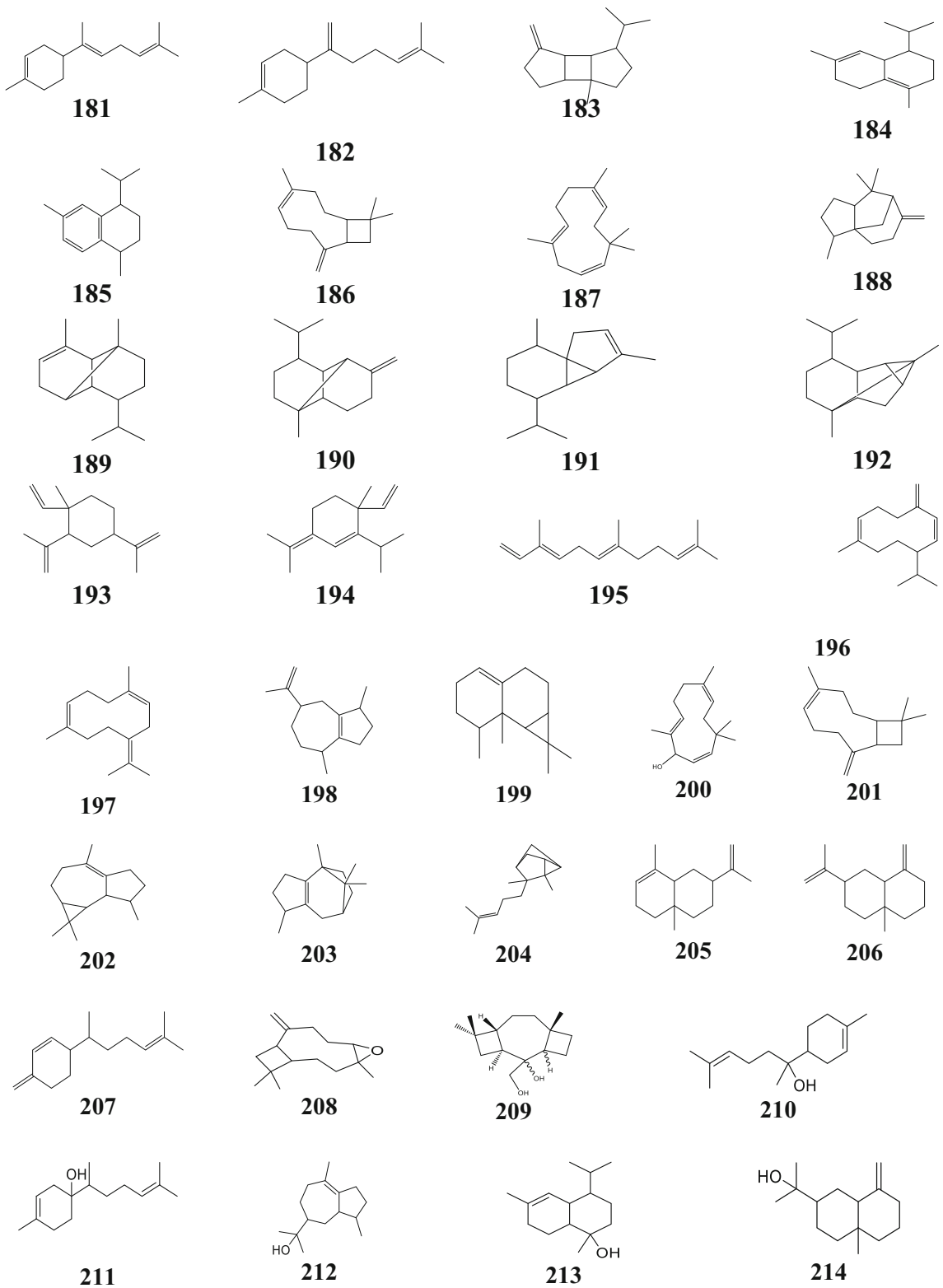

Fig. 8 continued

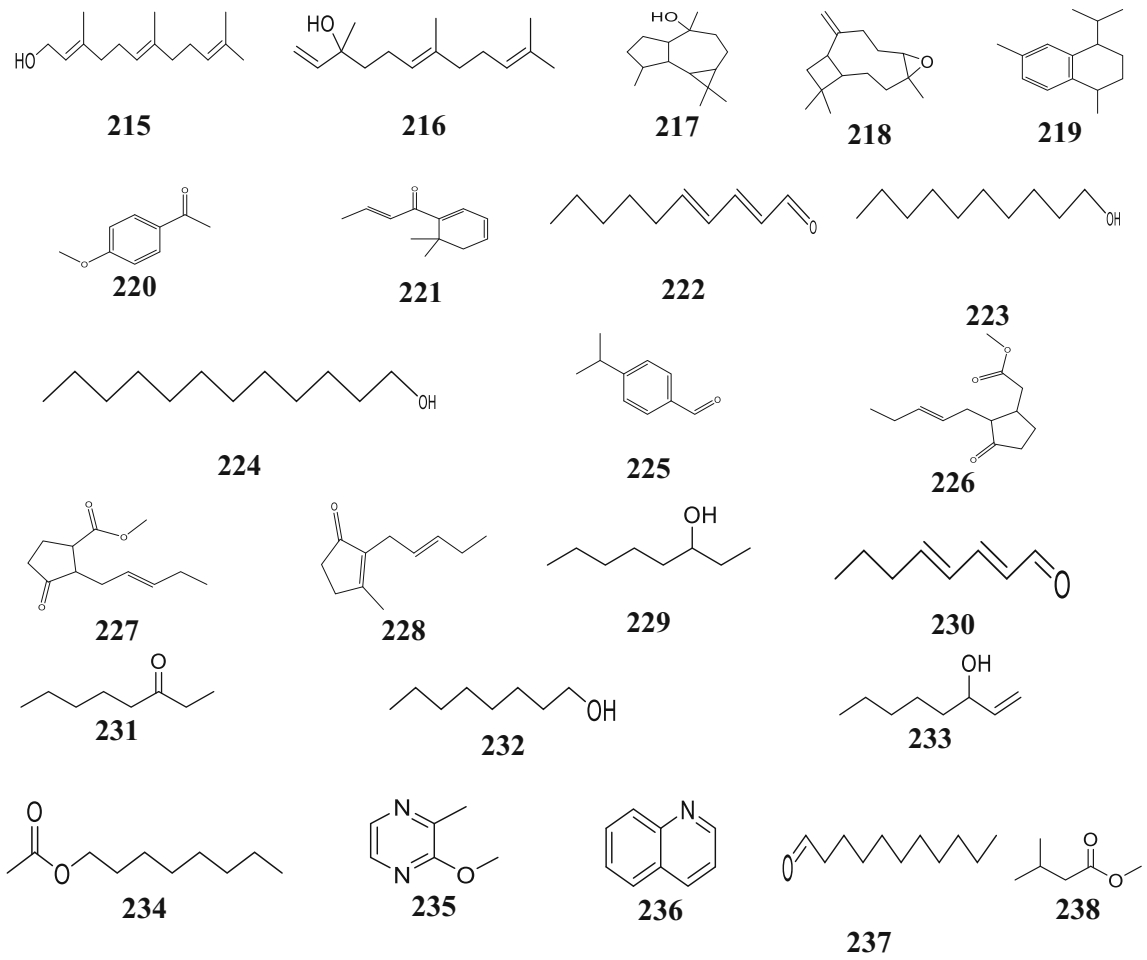

Fig. 8 continued

Furthermore, Rosmarinic acid (RA) 100 (with a safe oral LD_{50} up to 100 mg kg^{-1} in rats) was investigated for neuraminidase (NA) protecting potential of cells from destruction during H1N1 viral replication and gave IC_{50} of 16.65 ± 0.19, EC_{50} of 22.6 ± 2.76 and CC_{50} of ~ 200 µM. Molecular docking analysis revealed that the 3,4-dihydroxyphenyl moiety of caffeic acid is essential for the activity and suggested that the exploration of potent NA inhibitors from caffeic acid derivatives is promising to deal with influenza virus and that the two units of caffeic acid moiety definitely exhibit strong NA inhibitory activity (Bang et al. 2016). SAR analysis indicated that at least one carboxylic acid moiety and a bisphenol, as caffeoyl (3,4-dihydroxycinnamoyl) or galloyl (3,4,5-trihydroxybenzoyl), are necessary for the anti-HIV activity, while removal of the carboxylic acids or replacement with either cyclic or acyclic alkyl groups resulted in a comparable in vitro HIV-IN inhibition and no antiviral activity. The antibacterial activity of hydroxybenzoic acids was found to decrease with an increasing number of hydroxyl groups in correlation with their lipophilicity, while that of hydroxycinnamic acids doesn't depend on the substitutions of the aromatic ring with hydroxyl or methoxy groups, but is strongly dependent on the double bonds of the side chain (Sánchez-Maldonado et al. 2011).

Biosynthesis

Phenolic compounds are formed via the shikimate pathway, with shikimic acid as the main resulted

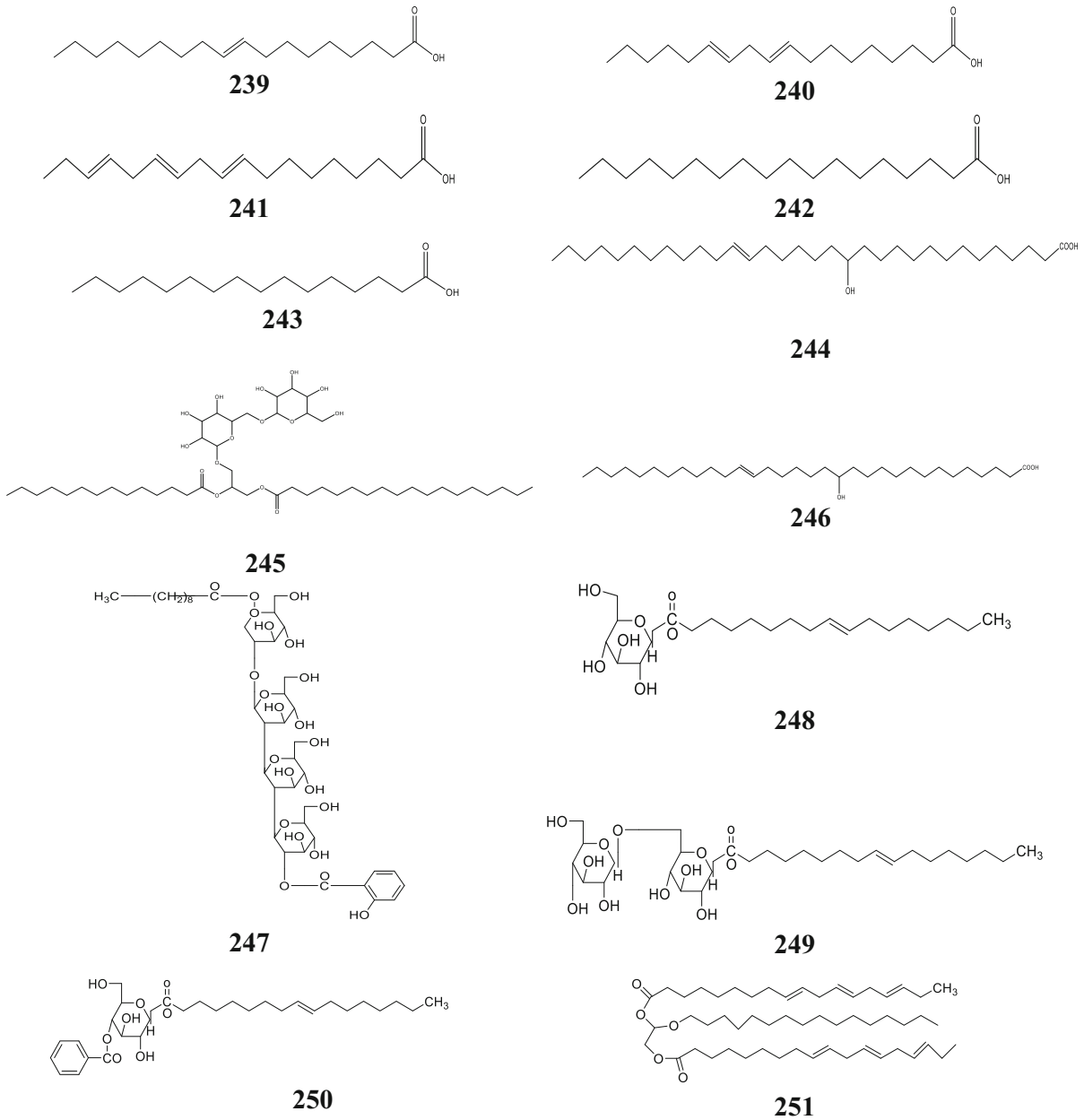

Fig. 9 Chemical structures of fixed oils

metabolite. The pathway consists of seven reaction steps, beginning with an aldol-type condensation of phosphoenolpyruvic acid (PEP) from the glycolytic pathway, and D-erythrose-4-phosphate, from the pentose phosphate cycle, to produce 3-deoxy-D-arabino-heptulosonic acid 7-phosphate (DAHP). A key branch-point compound is chorismic acid which is considered to be the final product of the shikimate pathway (Santos-Sánchez et al. 2019).

Bioavailability

Benzoic acid derivatives, as gallic acid, are well absorped after being methylated or glucouronated

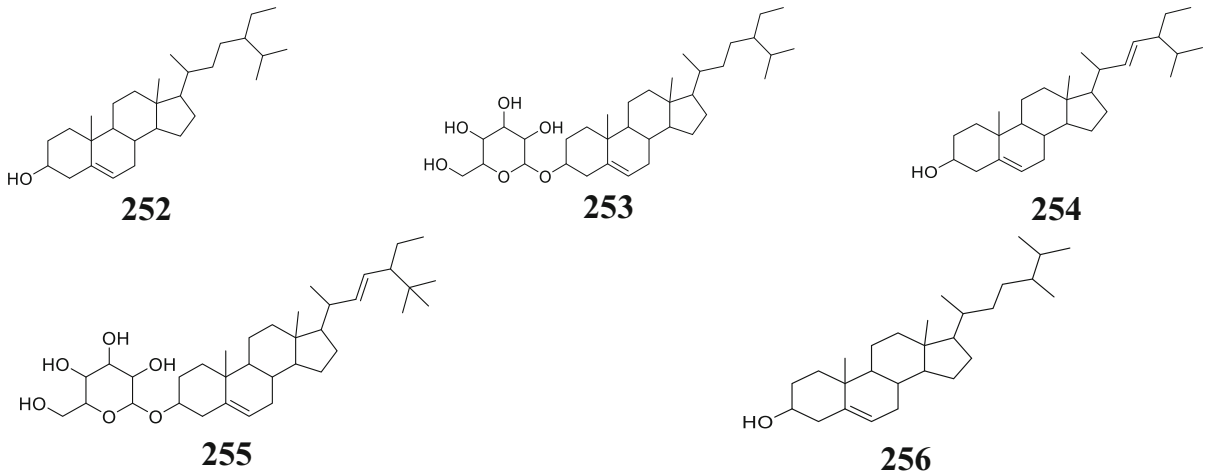

Fig. 10 Chemical structures of sterols

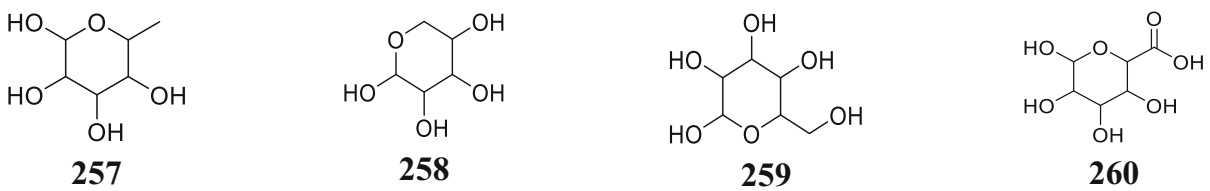

Fig. 11 Chemical structures of polysaccharides

(Shahrzad et al. 2001). Both chlorogenic and chicoric acids were cleaved by microbial esterase, hydrolyzed to caffeic acid (CA) and then reduced to dihydrocaffeic acid, which was then dehydroxylated to *m*-hydroxyphenylpropionic acid (Qiang 2011). On the other hand, cinnamic acid derivatives, as Ferulic acid, when supplemented to rats gave T_{max} reached 30 min of the acid with a reduction of bioavailability of sulfoconjugates after esterification (Adam et al. 2002). Comparing the bioactivity of CA with RA, after oral administration to rats at 100 μM kg^{-1} BW, gave a 9.7-fold higher absorption efficacy in the former than that of the latter (Konishi et al. 2005).

Amongst the 41 phenolic compounds detected in *Ocimum*, 32 compounds gave a wide range of biological activities while the other nine were inactive. Gallic acid methyl ester was considered as the most potent and highly significant ($P < 0.001$) antibacterial phenolic compound (Mondal et al. 2009), while rosmarinic acid was a potent ($P < 0.05$) antiviral one. Both citrusin C and lithospermic acid exhibited a significant capacity ($P < 0.05$) to suppress NO, while Ferulaldehyde was the most potent leishmanicidal compound ($P < 0.001$) isolated from the genus, followed by bieugenol ($P < 0.01$). Considering the field of apoptosis, Syringin was highlighted as the most active and highly significant ($P < 0.001$) anti-apoptotic bioactive compound isolated from the genus exhibiting about 0.98 ± 0.02 and 0.90 ± 0.01 folds suppression of neuronal toxicity leading to apoptosis at concentrations of 5 and 20 μM, respectively (US et al. 2015).

Anthocyanins

Eight anthocyanins 108–115 (Fig. 5) of both the cyanidin- and peonidin-based types were purified in 1998 from crude extracts of *O. basilicum* leaves, where they showed attractive antisickling activity (Phippen and Simon 1998). Anthocyanins are polyphenolic compounds abundantly found in plants as well as different types of foods (Panche et al. 2016). The total extractable anthocyanins yield among commercial purple basil cultivars ranged from (6.5 ± 1.1 mg 100^{-1} g FW) in Purple Bush and small leafed cultivar to (18.7 ± 0.8 mg 100^{-1} g) in

Dark Opal, Purple Ruffles and large leafed cultivars (Phippen and Simon 1998).

Biosynthesis

From a biosynthetic point of view, both flavonoid 3′-hydroxylase and flavonoid 3′,5′-hydroxylase catalyze the hydroxylation of dihydrokaempferol to form (2*R*,3*R*)-dihydroquercetin and dihydromyricetin, respectively. Both enzymes determine the hydroxylation pattern of the B-ring of flavonoids and anthocyanins for cyanidin and delphinidin production, respectively, together with being the key enzymes determining the structures of anthocyanins and specifying their colours (Tanaka et al. 2008). After oral administration, they could be absorbed from the stomach or intestine and appear in the bloodstream in 6–20 min after consumption to reach maximum levels after 15–60 min. Anthocyanins such as cyanidin-3-glucoside could be absorbed in its intact form into the GI wall, undergo extensive first-pass metabolism and enter the systemic circulation as Phenolic acid metabolites which were found in the blood stream in much higher concentrations than their parent compounds. These metabolites could be responsible for the associated health benefits (Fang 2014; Pojer et al. 2013).

Out of the eight detected anthocyanins, only two proved bioactivity, while the other six were considered inactive. Cyanidine-3-glucoside is one of the most potent apoptotic agents isolated from *Ocimum* which could, at a concentration of 10 μM tested for 48 h in comparison with Doxorubicin as a control, modulate the expression of caspase-3 and PARP in HS578T cells, inhibit tumor cell growth, induce apoptosis in vitro and suppress tumor growth in vivo as determined by western blot analysis ($P < 0.001$) (Chen et al. 2005).

Coumarins

Four coumarins 116–119 (Fig. 6) were isolated from the genus *Ocimum*, where Aesculetin 117, Aesculin 118 and coumarin 116 are the most bioactive ones (Yordi et al. 2017). Aesculin 118 displayed a significant antioxidant activity with IC_{50} 4.7 and 1.35 μM in DPPH and superoxide anion radical assays, respectively, in comparison with BHA as the control with IC_{50} of 32.4 and 72.9 μM, respectively (Lee et al. 2007). Aesculetin 117 exhibited a significant cytotoxicity on the viability and apoptosis of leukemia cells as determined by MTT assay, cell cycle analyses, DNA fragmentation, and chromatin condensation. The results revealed that concentrations of 0–225 μM of the compound administered for 24 h could inhibit the U937 cells growth compared to K562 and HL-60 cells (α-tubulin was used as internal control) (Chu et al. 2001).

Biosynthesis

A cytochrome P450 reaction is involved in the biosynthesis of coumarins which originate from the phenylpropanoid pathway with an ortho-hydroxylation of hydroxycinnamic acids as a fundamental step that has received inadequate attention in literature (Bourgaud et al. 2006). After oral administration of 120 mg kg^{-1} of both Aesculin and Aesculetin, the mean C_{max} values were 340.3 and 316.5 ng mL^{-1}, respectively. The bioavailability of esculin was calculated to be 0.62% (Rehman et al. 2015).

Terpenoids

Terpenoids (compounds 131–238) are the major class of compounds prevailing in the genus *Ocimum*, which are divided into: Triterpenes 120–130 (Fig. 7), monoterpenes, diterpenes, and sesquiterpenes 131–238 (Fig. 8). Monoterpenes are generally found in oils of aromatic plants especially in the *Lamiaceae* which encounters most of the terpenoidal compounds occuring in plants in nature as *Mentha*, *Rosemary* and *Thyme* (Singh and Chaudhuri 2018).

Triterpenes

The quantification studies highlighted Ursolic acid (UA) 120 (ursane-type triterpene, with oral LD_{50} 9.26 g kg^{-1} in mice), as the most prevalent compound within the genus with 0.252–0.478% w/w and 0.62–19.10 mg g^{-1} using HPTLC and UPLC-ESI–MS/MS, respectively (Prabhu et al. 2009). It possesses a wide range of activities, where it showed a significant antiproliferative action against MCF-7 human breast cancer cells, with the maximum effect obtained with 15 and 20 μM (about 30–40% of increase with respect to control). The mechanism of antiproliferative action was proposed to occur by inducing autophagy

and apoptosis, and in vitro suppression of inflammatory responses via the PI3K/AKT and NF-$_K$B signaling pathway (Luo et al. 2017). A further study examined the SAR of UA which revealed that the triterpenes possess two hydrogen-bond forming groups (an H-donor and a carbonyl group) at positions 3 and 28 which are responsible for the cytotoxic activity. Such activity concerns with the configuration at C-3, at which the introduction of an amino group greatly increases the potency up to 20 times than the parent UA, while selectivity greatly increases in the 28-aminoalkyl dimer compounds (Ma et al. 2005). Moreover, UA also proved an anti HIV-1 protease efficacy with IC_{50} value of 8 μM, and a potent leishmanicidal activity against *L. major* with IC_{50} of 4.95 μM (compared to amphotericin B as a control with IC_{50} 0.09 μM) (Suzuki et al. 2009).

On the other hand, the six triterpenic acids: UA 120, 3-epimaslinic acid 122, Oleanolic acid 124, Alphitolic acid 125, Betulinic acid 127 and Euscaphic acid 128 showed a significant hepatoprotective potential against CCl_4-induced oxidative stress, and gave a % inhibition ranged from 52.7 ± 15.7 to 56.8 ± 1.6% at MIC 0.22 μM when compared to silymarin as the positive control (Marzouk 2009). One of the bioactive compounds detected in *Ocimum* is Oleanolic acid 124, (LD_{50} 1500 mg kg^{-1} i.p. mice) which was considered a highly significantly active cytotoxic compound which was Brine shrimp lethality-tested against a panel of seven human solid tumor cell lines: lung carcinoma, breast carcinoma, colon adenocarcinoma, renal carcinoma, prostate adenocarcinoma, pancreatic carcinoma and yellow fever mosquito larvae *Aedes aegypti,* and gave ED_{50} values of 7.11, 5.5, 7.02, 7.04, 5.8, 7.8 μM, and LC_{50} of 0.15 μM, respectively. Such results were compared to adriamycin as positive control which obtained ED_{50} values 0.04, 0.78, 0.08, 0.098, 0.075, 0.017 μM, and LC_{50} 2.27×10^{-1}, respectively) (Njoku et al. 1997).

The inclusive SAR of the previous triterpenes revealed that they possess two hydrogen-bond forming groups (an H-donor and a carbonyl group) at positions 3 and 28 which exhibited cytotoxic activity, especially the configuration at C-3 which proved a great influence on the activity (Prabhu et al. 2009).

Biosynthesis

Triterpenoids and sesquiterpenoids are biosynthesized via the mevalonate pathway, whereas monoterpenoids, diterpenoid, and tetraterpenoids are biosynthesized via the methylerythritol phosphate pathway. Generally, a cyclization of 2,3-oxidosqualene is catalyzed by oxidosqualene cyclase oxidation, then further modifications occur via glycosylation (Sawai and Saito 2011). In the western world, the individual average human consumption of triterpenes is estimated, and found to be approximately 250 mg day^{-1}, and reached up to 400 mg day^{-1} in the Mediterranean countries. Both Betulinic and oleanolic acids are fairly absorped from the GIT, so derivatives have been synthesized to improve permeability to reach up to 4.9–32.7%.

Out of the 11 isolated triterpenes from the genus *Ocimum*, 8 compounds were reported to be bioactive while the other 3 had no reported activity. Ursolic acid was outlined as the king of bioactive triterpenes with a diversity of bioactivities. Although being a moderate hepatoprotective agent, it gave, as well as oleanolic acid, the highest significant results as cytotoxic one ($P < 0.001$) when compared to doxorubicin. It was also emphasized as the strongest both antiviral and antileishmanial triterpene with the least IC_{50} values, as previously mentioned.

Essential oils

About 107 different compounds (from 131 to 238) belonging to the essential oils were detected in the genus *Ocimum*. Many of them showed a wide range of bioactivities, where methyl eugenol 84 showed a significant leishmanicidal activity (IC_{50} = 9 μM and IC_{90} = 15.76 μM) (Zheljazkov et al. 2007b), while β-caryophylline oxide 208 exhibited a significant antiproliferative activity against MCF-7 cell line with IC_{50} 10.8 μM. (Compared with doxorubicin as the control with $IC_{50} < 0.2$ μM, Singh et al. 2014).

Biosynthesis

Essential oils are biosynthesized via two complex natural biochemical pathways: isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP) as the universal precursors, and they are produced by the cytosolic enzymatic MVA pathway or

by the MEP pathway. In the particular plant cell part, prenyl diphosphate synthases condense isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) further to form prenyl diphosphates, which are used as substrates for geranyl diphosphate (GPP, C_{10}) or for fernesyl diphosphate (FPP, C_{15}) (Rehman et al. 2016).

Bioavailability

Essential oils can be absorbed from the food matrices or as pure products and cross the blood brain barrier easily due to their lipophilic character and small size. When 10% aqueous solution of α-pinene, limonene, camphor and borneol was given orally to mice, the bioavailability obtained was 61%, 66%, 54%, and 58%, respectively, and when the same compounds were topically applied to skin shaved mice, no one was absorped preferably indicating that the oral bioavailability is better than the dermal one, besides the role of inhalation which provides the most efficient bioavailability results (Kohlert et al. 2000; Pattanayak et al. 2010; Djilani and Dicko 2012).

Out of all the simple terpenoids classified under the essential oils, 29 monoterpenes out of the detected 45 compounds had no reported activities up to date, and amongst the 44 isolated sesquiterpenes, 39 compounds were considered inactive. Regarding the most bioactive ones, methyl eugenol and α-cadinene gave the best ever leishmanicidal activity with nearly equal IC_{50} values. Moreover, both β-caryophylline and its oxide were highly significant antiproliferative agents against MCF-7 cell line with also nearly equal IC_{50} values (Ntezurubanza et al. 1984). On the other hand, essential oil extracted from *O. gratissimum* leaves proved a highly significant inhibition of *S. aureus* at MIC of 0.75 μg ml^{-1} and against *Shigella*, *Salmonella* and *E. coli* at MIC 3–12 μg ml^{-1}, compared with DMSO (100 μl) as a standard (Nakamura et al. 1999). The best ever cytotoxic results amongst the *Ocimum* bioactive fractions were assessed by the colorimetric SRB assay of the essential oil extracted from *O. viride* aerial parts, where they inhibited COLO 205 cells, with IC_{50} values of 0.070, 0.058 and 0.033 μg ml^{-1} at 24, 48, and 72 h, respectively. The results were highly significant ($P < 0.001$) when compared with DMSO as a control which didn't produce any efficacy (Sharma et al. 2010).

Fixed oils (fatty acids)

About 13 fatty acids and fatty acid derivatives (239–251) have been detected up to date in the genus *Ocimum* (available studies concerned only with *O. sanctum* and *O. basilicum*) over the period from 2002 to 2014 (Fig. 9). In general, most of them exhibited good antihypercholesterolemic properties, as well as other diverse bioactivities. Both Oleic acid 239 and Linoleic acid 240, which were isolated from *O. sanctum* seed oil (Mondal et al. 2009), proved efficacy as antimicrobial agents, and when they were SAR investigated, it was found that the number and position of double bonds as well as modifying the carboxyl group in their structures could greatly influence their activity (Huang et al. 2010). On the other hand, the antiarthritic potential of the fixed oils obtained from *O. sanctum* was investigated, and showed a significant inhibition of turpentine oil-induced joint edema in rats at a concentration of 3.0 ml kg^{-1}, i.p. at 1, 2, 3, 4, and 5 h compared with aspirin as control (100 mg kg^{-1}) (Singh and Majumdar 1996).

A further related study reported that the antiulcer potential of *O. sanctum* seed oil could probably be due to its anti secretory effects (Bilal et al. 2012). Concerning antihypercholesterolemic potential of that oil, it significantly reduced serum cholesterol, triacylglycerol, LDL, VLDL and cholesterol in cholesterol fed rabbits, at a concentration of 0.8 g kg^{-1} day^{-1} for 4 weeks (dose 100 mg kg^{-1} day^{-1}). Interestingly, two new fatty acid derivatives (cerebrosides), Ocimumoside A 244 and Ocimumoside B 245 were purified in 2007 from *O. sanctum* leaves extract, and were found to possess strong antistress activity (Gupta et al. 2007).

Biosynthesis

Fatty acids (FA) naturally occur in the two subcellular compartments: chloroplasts and endoplasmic reticulum (ER). Both de novo synthesis from acetyl-CoA of such FAs, as palmitic or stearic as well as desaturation of stearic acid to oleic acid, occur in plastids, whereas the further conversion of oleic acid into linoleic acid and further to linolenic acid occurs in the ER (Sidorov and Tsydendambaev 2014).

Bioavailability

A great variation in absolute bioavailability occurs after oral administration of some FAs to rats. α-Linolenic acid was rapidly absorbed (0.76 h) and distributed when given in a dose of 31 mg kg^{-1} body weight, while the absolute oral bioavailability was 0.7% after oral doses of 25 and 50 mg kg^{-1} of oleanolic acid, indicating poor absorption and extensive metabolism in vivo (Rodríguez-Alcalá et al. 2015; Cholewski et al. 2018).

Amongst the 13 detected FAs, 6 were active and the other 7 had no reported activities. In general, linolenic and palmitic acids were considered as highly significant bioactive antibacterial agents ($P < 0.001$) while oleic and linoleic acids were well marked antiulcerogenic ones ($P < 0.05$). The two cerebrosides A and B were emphasized as significant ($P < 0.05$) anti stress compounds among all the antistress and immunomodulatory compounds isolated from the genus.

Sterols

Five sterols and sterol derivatives 252–256 were isolated from the genus *Ocimum* over the period form 1961 to 2012 (Fig. 10), among them were β-sitosterol, stigmasterol and daucosterol which possess diverse bioactivities. β-Sitosterol 252, with oral LD_{50} more than 25 g kg^{-1} in mice, was synthesized from stigmasterol 254 via selective hydrogenation of the side chain Δ 22–23, and biosynthesized from both mevalonate and deoxyxylulose pathways which is regulated during membrane biogenesis. Both β-sitosterol 252 and stigmasterol 254 (1.8-fold stronger than β-sitosterol) possesses the capability to bind to chondrocyte membrane and exert a series of anti-inflammatory and anti-catabolic actions at a concentration of 45 μM via counteracting expression of the MMPs involved in cartilage degradation as well as inhibiting the pro-inflammatory mediators PGE2 via counteracting the NF-$_K$B pathway (Gabay et al. 2010).

Biosynthesis

The usual pathway of sterol biosynthesis proceeds along the well-established isoprenoid trail passing from the "active isoprene unit", through isopentenyl diphosphate, to the C_{30} triterpenoid squalene via three major stages: acetate → isoprenoid intermediate → cyclization product → cholesterol and with the aid of acetoacetyl CoA thiolase, hydroxyl-3-methylglutaryl CoA synthase, 3-hydroxy-3-methylglutaryl CoA reductase, phosphomevalonate kinase and finally mevalonate diphosphate decarboxylase. As a result, C_{30} symmetric olefin is formed, followed by oxidation to form *S*-oxidosqualene via an NADPH-dependent mono-oxygenase reaction catalyzed by squalene epoxidase (SQE), and this substrate can be cyclized by an oxidosqualene–sterol synthase to yield the steroidal backbone structure represented in lanosterol which is further converted into cholesterol (Nes 2011).

Bioavailability

Phytosterols are generally poorly absorpable, and it was stated that less than 10% of dietary phytosterols are systematically absorbed, in contrast to about 50–60% of dietary cholesterol (Ogbe et al. 2015).

Polysaccharides

A polysaccharide fraction (constituted of 23.3% of rhamnose 257, 19.2% of xylose 258 and 10.3% of glucose 259) was detected in *O. basilicum* seeds (Anjaneyalu and Gowda 1979) (Fig. 11). The fraction isolated from mucilage of *O. canum* contained the same constituents but with different concentrations, where D-glucose, D-mannose, D-galactose, L-arabinose, D-xylose and L-rhamnose have existed in the approximate ratio 8:5:2:1:1:2 (Anjaneyalu and Tharanathan 1971). In the same context, the mucilaginous capsular polysaccharide-complex isolated from the seeds of *O. gratissimum* yielded an acidic xylan composed of D-xylose (48%), L-arabinose (16%), D-galactose (16%), and D-galacturonic acid (∼ 20%) (Anjaneyalu et al. 1983). Polysaccharide fraction of *O. basilicum* exhibited a potent DPPH free radical scavenging activity with $IC_{0.2}$ 11.26 μM compared to α-tocopherol ($IC_{0.2}$ value of 11.9 ± 0.2 μM) and BHA ($IC_{0.2}$ value of 14.5 ± 2.5 μM), while the % inhibition at both concentrations (20 and 40 μg ml^{-1}) were 60.7 ± 4.1% and 76.6 ± 3.8%, respectively (Subramanian et al. 2005). In the same context, it inhibited the lipid peroxidation at IC_{50} 12.6 μM in a significant and a concentration-dependent manner where it showed 39.1 ± 4.5% and 80.3 ± 4.5% protection in AAPH and Fe(II)-ascorbic acid induced

lipid peroxidation, respectively. The results revealed that effectiveness of the fraction in the Fe(II)-ascorbic acid system with IC_{50} 30.18 μM was far superior to that in the AAPH system with IC_{50} 78.6 μM (Subramanian et al. 2005). In addition, the polysaccharide fraction isolated from *O. sanctum*, at 100 μg ml^{-1}, protected 30 ± 3.2% mouse splenocytes against γ-ray irradiation, the activity which was explained by the presence of reactive oxygen species scavenging and iron chelating properties (Singh and Chaudhuri 2018).

Nutraceutical value (minerals, pigments and mucilage)

Minerals in routine dietary intake play an important role in food and nutraceutical industry. In the same context, herbs of *Ocimum* which have been used to add distinctive flavor to food have also been used as a home remedy for various health conditions. In addition, they have been considered as rich sources of vitamins, minerals, fats, proteins, polysaccharides, fibers, pigments and mucilage. Interestingly, the elemental analysis of macro and micro contents of *O. sanctum* leaves using LIBS and ICAP-AES techniques revealed the presence of elements as C, H, O and N which suggest its application in maintaining electrolytic balance and obtaining organic compounds. The same study also showed the presence of vitamin A, vitamin C, β-carotene, ribiflavone, chlorophyll, insoluble oxalates, proteins (30 kcal), fats (0.5 g), carbohydrates (2.3 g) and minerals (Tripathi et al. 2015). Each 100 g of *O. sanctum* leaves contains vitamin C (83 μg), carotene (2.5 μg), Ca (3.15%), P (0.34%), Cr (2.9 μg), Cu (0.4 μg), Zn (0.15 μg), V (0.54 μg), Fe (2.32 μg) and Ni (0.73 μg) (Pattanayak et al. 2010). Besides, ascorbic acid (8.21 mg), riboflavin (0.06 mg) and thiamine (0.3 mg) contents which suggest its leaves intake as an edible plant to be a dietary supplement and an alternative economic source of vitamins and natural antioxidants (Bhattacharya et al. 2014). Similarly, the seed mucilage of *O. sanctum* (yield ~ 30%) contains hexouronic acid (27.25%), pentoses (38.9%), protein and amino acids (Hameed et al. 2016). In the same context, *O. basilicum* contains high amounts of such minerals where 100 g of fresh plant contains Mg (64 mg), K (295 mg) and Fe (3.17 mg). The plant is also rich in a variety of important nutrients, where a 100 g fresh plant was found to contain vitamin A (264 μg), vitamin C (18 mg), riboflavin (76 μg), vitamin K (414 μg), Ca (177 mg) and P (56 mg) (Filip 2017). A related study concerned with *O. gratissimum* revealed that each 100 g of powdered leaves or stems of the plant contained Ca (5.2 and 3.73 mg l, s), Mg (0.53 and 0.33 mg l, s), Fe (13.9, 6.76 mg l, s) and P (4.25 and 3.05 mg l, s). 3.33 ± 0.07% and 1.65 ± 0.02% crude protein content for leaves and stems; 8.50 ± 0.04% and 3.00 ± 0.15% crude lipid content for leaves and stems and 9.52 ± 0.01% and 19.65 ± 0.03% crude fiber content for leaves and stems.

Accordingly, the nutraceutical value of the studied *Ocimum* species arise from the biological importance of such elements, as Mg and K which are considered among the seven essential macrominerals improving the health of cardiovascular system and transmission of nerve impulses, as well as providing protection from a number of chronic diseases. Moreover, the higher K content in the stems also qualify the plant to be efficient for hypertensive patients, the polyphenolics play an important role as powerful antioxidants and the presence of different minerals play an important role in proper tissue functioning (Idris et al. 2011).

Chemical difference between *Ocimum* species

The variation in the essential oil content and chemical composition of the leaves and inflorescences of most *Ocimum* species were determined for two harvesting seasons. The essential oil extracted using hydrodistillation and chemical characterization was performed using GC/MS techniques, and the recovery ranged from 0.18 to 0.774% during pre-monsoon and 0.141–0.748% during post-monsoon. Out of the different analyzed species, *O. gratisimum* showed the highest percentage of eugenol (53–89%), followed by *O. santum* 'Purple and green varieties' while *O. viride* and *O. gratisimum* were rich in methyl isoeugenol (40.26–53.21%). Analyzing the flavonoidal profile of the nine studied species of *Ocimum*, substantial infraspecific differences were found. For example, *O. americanum* var. *pilosum* accumulated the flavone *C*-glycoside, vicenin-2, which existed in var. *americanum* in traces. The major flavonoids found in all the investigated species were flavonol 3-*O*-

glucosides and 3-*O*-rutinosides, while many other species produced the more unusual compound, quercetin 3-*O*-(6-*O*-malonyl) glucoside, and small amounts of flavone *O*-glycosides. The level of flavonol glycosides was significantly reduced in glasshouse-grown plants, but the levels of flavone glycosides were unaffected. *O. sanctum* was characterised by the accumulation of flavone-*O*-glycosides as the 7-*O*-glucuronides of luteolin and apigenin, while Luteolin 5-*O*-glucoside, which was found in all nine species of *Ocimum* studied, and is considered to be a key character for the genus (Grayer et al. 2002).

In general, it seems that the high degree of polymorphism within the genus *Ocimum* evoked a large number of subspecies and different varieties with varying chemical composition, which offers a variable level of medicinal potential.

Conclusion and future perspectives

Keeping the various medical benefits together with the ancient traditional uses of many *Ocimum* species, several studies have been carried out towards discovery of the bioactive components (Fig. 12). Two hundred and sixty compounds were reported from the genus *Ocimum* over the period from 1961 to April 2019, 100 of them have been isolated in the period from 2001 to 2010 (Fig. 13). Our research results highlighted O. *Sanctum, O. gratissimum* and *O. basilicum* as the most well-studied species with the most well-known traditional uses and chemopharmcological importance (Table 2). However, other *Ocimum* species such as *O. viride*, *O. americnum* and *O. canum* are underexplored and need more chemical and biological investigations. Different classes of compounds including phenolics, flavonoids, neolignans, terpenoids, coumarins and fatty acid derivatives were discovered, with terpenes and flavonoids as the major prevailing classes of compounds which are responsible for most of the genus bioactivities (Fig. 1). Among those valuable bioactive compounds, essential oils isolated from different *Ocimum* species provided good sources of natural eugenol and a high commercial importance in pharmaceutical, cosmetics and food industry. In addition, they have been a new lead for prevention and treatment of hyperglycemia, atherosclerosis and serious cardiovascular disorders. Concerning flavonoids as the second prevalent class, orientin and vicenin which showed a significant radioprotection to human peripheral lymphocytes were suggested for clinical application in cancer radiotherapy and as a new choice for the treatment of UT bacterial infections, with the need for further investigation to ensure complete safety. On the other hand, the fixed oil of seeds which is rich in ω-3 fatty acids is considered as of recent interest of most researchers, due to its wide range of pharmacological properties especially in cardioprotection. The review highlighted *O. sanctum* as the "Queen of herbs" with a wide range of biological activities discovered by the traditional users, in particular the immunomodulatory

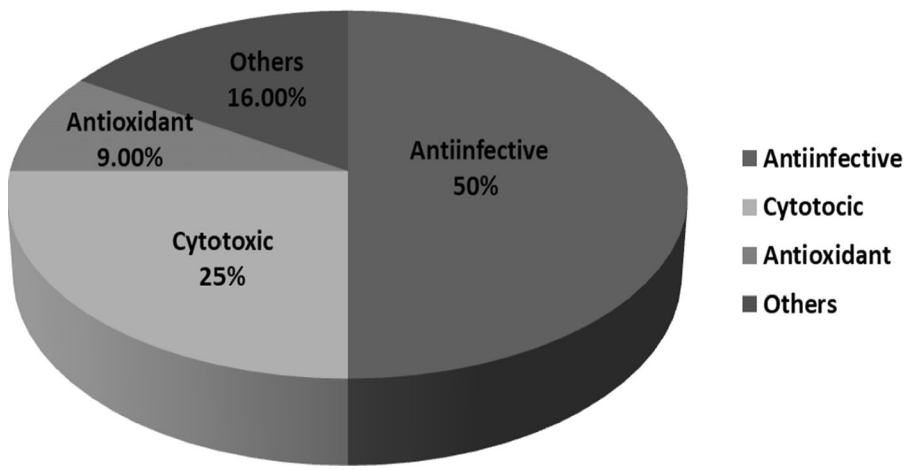

Fig. 12 Bioactivity profile of the compounds isolated from *Ocimum*

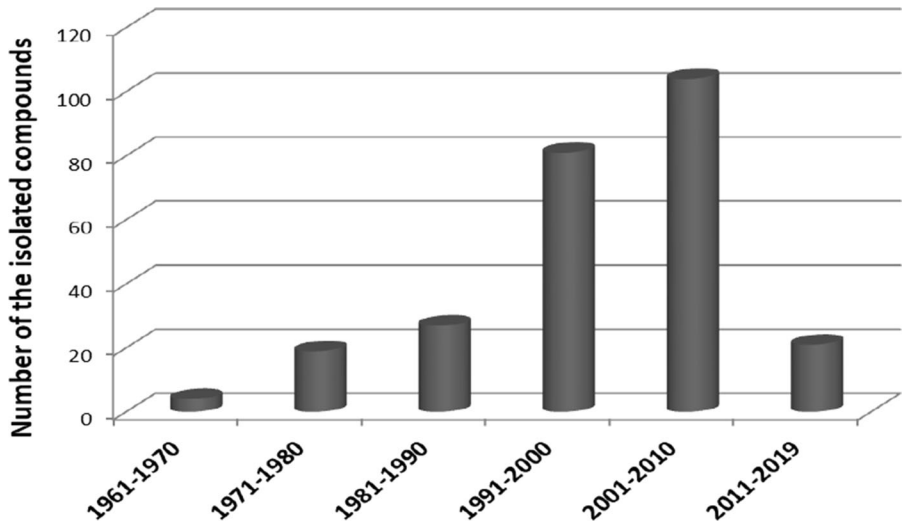

Fig. 13 Number of metabolites isolated from different species of the genus *Ocimum* over the period 1961–April 2019

and adaptogenic ones, which were further confirmed by pre-clinical studies and finally tagged with the clinical ones, and which could opportunely provide more assurance on the efficacy coupled-safety of *Ocimum* as a herbal remedy.

Nevertheless, analysis of the reviewed data has revealed some considerable gaps in studying *Ocimum*. Firstly, some species as *O. canum, O. suave* and *O. forskolei*, with a plenty of phytonutrients and a considerable history of folkloric uses, have been insufficiently investigated and mainly limited to insect repellent activity studies. Additionally, roots and stems of the genus *Ocimum* have also been chemically and biologically underinvestigated. In general, there is a need for further investigation of the chemical aspects of *Ocimum* to get novel molecules with new pharmacological potentials. More SAR studies are needed to illuminate the possible mechanisms of action of the isolated compounds as antitumor, antiviral, gastroprotective and anti-inflammatory agents. Additionally, new approaches such as metabolomics based on HRMS and NMR data could be applied to compare the various species of *ocimum* and to correlate chemical diversity to biological potential. Moreover, several aspects are also needed to work on the large scale plans to isolate sufficient amounts of the major as well as the minor chemical constituents to explore their pharmacological activities. Furthermore, synthetic analogues of bioactive metabolites of *Ocimum* should be developed to focus on improving their efficacy and safety.

Despite the lack of long-term clinical trials, the 24 studies published to date have suggested that Tulsi is a safe herbal intervention that may assist in normalising blood glucose, blood pressure and lipid profiles and which can fight psychological and immunological disorders. In the same context, the studies indicated that daily addition of Tulsi to the diet and/or as adjunct to drug therapy can potentially assist in prevention or reduction of various health conditions, the results which really warrants further clinical evaluation. Finally, more efforts should be directed towards the investigation of these species to translate them into existing market products which may be potentially beneficial, in addition to be less toxic than currently available synthetic compounds to enable *Ocimum* plants to contribute a lot towards economy and health care.

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Compliances with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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