Chapter 14
Bioactive Metabolites from Fungi with Anti-Inflammatory and Antithrombotic Properties: Current Status and Future Perspectives for Drug Development

Alexandros Tsoupras and Kyeesha Glenn Davi

Abstract Bioactives of natural origin have recently gained a lot of ground in drug discovery due to their enormous structural diversity, diverse pharmacological activities, safety, and inherent binding capacity with other biomolecules. However, the high demand for new agents for the prevention and therapy of inflammation-related chronic disorders has not yet been sufficiently addressed by the drug discovery process. This gap highlights the relevance of intensifying studies to reach sustainable employment of the huge world biodiversity, such as microorganisms, including fungi of biotechnological and agro-food medical interest that can be easily cultured/engineered as sustainable sources of natural bioactives for drug development. Thus, fungi are important sources of such bioactive compounds studied and applied for different purposes, specifically, in the pharmaceutical area, such as the development of antibiotics, immunomodulators, immunosuppressants, enzyme inhibitors, and antiviral, hypercholesteremic, antineoplastic/antitumor, and anti-inflammatory agents. Within this chapter, several examples of bioactive metabolites produced by different fungi species with proven pharmacological effects and beneficial anti-inflammatory and antithrombotic potential are thoroughly reviewed. After recent updates in the field of "omics" and "one strain many compounds" (OSMAC) approaches, within this chapter the emerging use of fungal endophytes as strong unconventional sources of biologically active natural compounds with many producing pharmacologically valuable specific plant-derived anti-inflammatory products is also presented. Overall, this chapter explores the current and future perspectives of the use of fungal metabolites with potent anti-inflammatory and antithrombotic properties and subsequent health benefits with potential pharmaceutical applications as supplements and/or drugs.

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1 Introduction

Inflammation is a complex biological reaction by which the human body responds to tissue damage and to various harmful stimuli, including toxic compounds, damaged cells, and infectious agents and pathogens. In addition, inflammation plays a vital role in tissue repair and regeneration toward homeostasis (Tsoupras et al. 2018). Generally, acute and controlled inflammation is beneficial, while unresolved and chronic inflammatory response can occur due to the continuous and unresolved presence of the triggering agent(s) and risk factors, and due to a subsequent inappropriate immune response, that usually results in further tissue injury, destruction, and several other harmful inflammatory manifestations (Tsoupras et al. 2018).

Thus, it has now been well established that unresolved and chronic inflammation and its thrombo-inflammatory manifestations are major causes of several chronic disorders (Tsoupras et al. 2018; Furman et al. 2019), such as atherosclerosis and cardiovascular diseases (CVD) (Tsoupras et al. 2018, 2019; Furman et al. 2019), renal (Tsoupras et al. 2007, 2018), and neurodegenerative disorders (Tsoupras et al. 2018), tumor and metastatic procedures (Tsoupras et al. 2018; Tsoupras et al. 2009; Lordan et al. 2019), asthma, allergy and several autoimmune diseases (Tsoupras et al. 2018), and persistent infections, including HIV infection (Tsoupras et al. 2012a), SARS-COV-19 infection (Tsoupras et al. 2020a; Zabetakis et al. 2020), periodontitis (Tsoupras et al. 2006; Antonopoulou et al. 2003), sepsis (Tsoupras et al. 2011a), and their associated inflammatory conditions and comorbidities (Tsoupras et al. 2018). Interestingly, the presence of one or more of such pathological conditions further triggers and propagates the co-development of other ones through further inflammatory activation and a subsequent vicious cycle of inflammatory, thrombotic, and oxidative manifestations (Fig. 14.1) (Tsoupras et al. 2018, 2019, 2007, 2009, 2012a, 2020a, 2006, 2011a; Furman et al. 2019; Lordan et al. 2019; Zabetakis et al. 2020; Antonopoulou et al. 2003).

Several compounds of natural and/or synthetic origin with anti-inflammatory actions have been extensively studied for potential benefits and amelioration of the inflammatory burden in these disorders, with natural bioactives being on the hotspot lately, especially for the food/feed supplements and drug industries (Tsoupras et al. 2018, 2007, 2009, 2020a, b, 2022a, b, c, 2011b; Lordan et al. 2019; Zabetakis et al. 2020, 2022; Conde et al. 2021; Glenn-Davi et al. 2022; Verouti et al. 2013; Karantonis et al. 2022). Natural products have been relevant sources for drug discovery and the development of medicines since ancient times. Several such bioactive compounds of natural origin have been found in plants, animals, or marine organisms, and microorganisms of different environments (aquatic, terrestrial, or air), with emphasis being given to natural bioactives derived from sustainable sources on a circular economy approach.

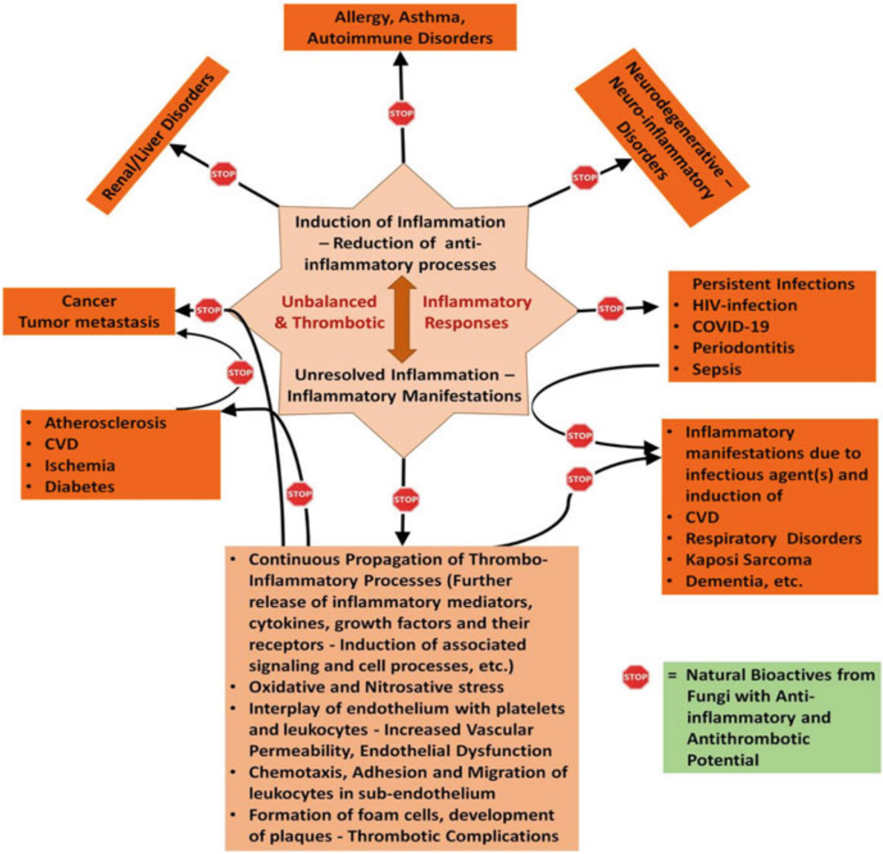


Fig. 14.1 Unbalanced inflammatory and thrombotic responses due to the presence/co-presence of several risk factors can lead to continuous and unresolved inflammation with subsequent thrombo-inflammatory manifestations that are implicated in the initiation, propagation, and development of several inflammation-related chronic disorders. Such thrombo-inflammatory processes are also implicated in the induction of a chronic disorder(s) due to the unresolved presence of another one of these disorders. Natural bioactives, and especially those from microorganisms of biotechnological and agro-food-medical interest, including fungi bioactives with anti-inflammatory and antithrombotic properties are potential candidates for drug development against inflammation, thrombosis, and the prevention of inflammation-related chronic disorders

Among these natural sources, the cultivation of microorganisms as sustainable sources for isolating their bioactive metabolites has gained ground in the drug and supplements industries. Attention has been given to microorganisms with low toxicity and well-established tolerance in human nutrition and other non-toxic applications, not only well-established ones used in fermentation processes, including yeasts for the production of fermented foods (Moran et al. 2021; Fragopoulou et al. 2004) and bacteria for bioethanol production (Tsoupras et al. 2012b), but also microorganisms used in other fields, such as fungi of bio-agro/food technological applications like those used as natural entomopathogenic agents for organic cultures (Tsoupras et al. 2022b).

Fungi are a group of heterotrophic and essentially aerobic, with limited anaerobic capabilities, and eukaryotic microorganisms (McGinnis and Tyring 1996). Fungi can occur as yeasts, molds, or as a combination of both forms. Yeasts are microscopic fungi consisting of solitary cells that reproduce by budding. Molds, in contrast, occur in long filaments known as hyphae, which grow by apical extension. Hyphae can be sparsely septate to regularly septate and possess a variable number of nuclei. Regardless of their shape or size, fungi are all heterotrophic and digest their food externally by releasing hydrolytic enzymes into their immediate surroundings (absorptive nutrition). Other characteristics of fungi are the ability to synthesize lysine by the L-α-adipic acid biosynthetic pathway and possession of a chitinous cell wall, plasma membranes containing the sterol ergosterol, 80S rRNA, and microtubules composed of tubulin.

Apart from these general properties of fungi, lately they have been proposed as a promising sustainable source of an enormous number of natural bioactives, which have made significant contribution to almost each sphere of human, plant, and veterinary life. Natural compounds obtained from fungi have proved their value in nutrition, agriculture, and healthcare. Primary metabolites, such as amino acids, enzymes, vitamins, organic acids, and alcohol, are used as nutritional supplements and in the production of industrial commodities through biotransformation (Singh et al. 2017). In addition, highly bioactive fungi compounds have also been found to be some secondary metabolites (SMs) of fungi, meaning organic biomolecules with a low molecular weight that form at the end or near the stationary phase of growth, and are not directly associated with growth, development, and reproduction of fungi. SMs are not only essential for the growth and development of their microbial producer, but they can also increase the tolerance of microorganisms to different types of environmental stresses and hostile conditions and, consequently, their survival rate. On this accord, and since the unanticipated discovery of antibiotic penicillin by Fleming in 1929, this has drawn the interest of scientists to investigate the therapeutic role of microbial products not only for combating life-threatening infections as antimicrobial and antiparasitic agents, but also for several other healthcare applications, such as their use as antitumor, anti-inflammatory, anticoagulant and antithrombotic agents, enzyme inhibitors, anabolics, hemolytics, hypocholesterolemics and vasodilators, anesthetics, anthelmintics, and immunosuppressants (Singh et al. 2017).

Bioactive SMs are produced mainly by fungi of soil microbiota, marine environments, or extreme environments, but also of underexplored niches, including plant-associated fungi called endophytes, which live in symbiotic relationships with host plants (Conrado et al. 2022). They usually are obtained by extraction and other separation procedures, and they are primarily used in the biopharmaceutical industry and as ingredients in functional foods due to their capability to reduce inflammatory and infectious diseases in human beings and animals and thus increase life expectancy (Singh et al. 2017; Conrado et al. 2022).

Health care is the largest end-user market for microbes like fungi and such beneficial microbial products, which reflects the importance of microbe-based biopharmaceutical industry (Singh et al. 2017). To date, among the approved SMs by the US Food and Drug Administration (FDA) for drug discovery, ~ 15% belongs to microbial origin. In microbial groups of fungi and their products, for example, enzymes, fermented foods, animal feed, antibiotics, pharmacy products, and pigments have contributed significantly to humans and many biotechnological industries, as well as for several other applications such as the use of SMs from a basidiomycetous fungus, for example, *Ganoderma lucidum* and *Trametes versicolor*, as flavoring compounds, in flavored coffee, and in cosmeceutical products (Shankar and Sharma 2022). In addition, recent research has demonstrated that among fungi species, the endophytes are a great source of bioactive SMs. These microorganisms have functional diversity and, in association with plants, can produce a plethora of SMs (Conrado et al. 2022).

Fungi-derived nutrients and bioactive compounds have great potential as ingredients of functional foods, supplements, and drugs, since they can exhibit various beneficial effects along with medicinal properties and additional health benefits, including anti-inflammatory effects. From the several applications of fungi metabolites within this chapter, the current status of the anti-inflammatory and antithrombotic benefits of several fungi bioactives will be extensively reviewed, with emphasis on compounds with potential use in the development of supplements and drugs for the prevention and treatment of a range of inflammatory disorders and associated chronic diseases.

2 Fungi as Sustainable Sources for Bioactive Compounds of Natural Origin

Fungi are a miscellaneous group of organisms comprising several beneficial and damaging biological activities, which have a major impact on flora and fauna of the biome. For example, fungi are known to produce some potent antibiotics such as penicillin and cephalosporin. On the other hand, some fungal species are able to synthesize and excrete extremely toxic metabolites, such as aflatoxins, curvularin, and helminthosporin. These filamentous fungi show huge diversity in their metabolites including lipids, polyketides, alkaloids, quinones, and carotenoids. The metabolic diversity of fungal genera is extraordinary, making it possible for them to produce metabolites with various biological activities such as antioxidant, anticancer, antiviral, antimicrobial, and anti-inflammatory (Mehta et al. 2022).

The optimum extraction of such natural bioactives from fungi can be performed by controlling and optimizing their growth conditions and using low-cost and fast approaches, thus representing an economically valid and biosustainable alternative production of natural bioactives for the development of supplements and drugs. Usually, the isolation of a fungi strain for the development of a pharmaceutical

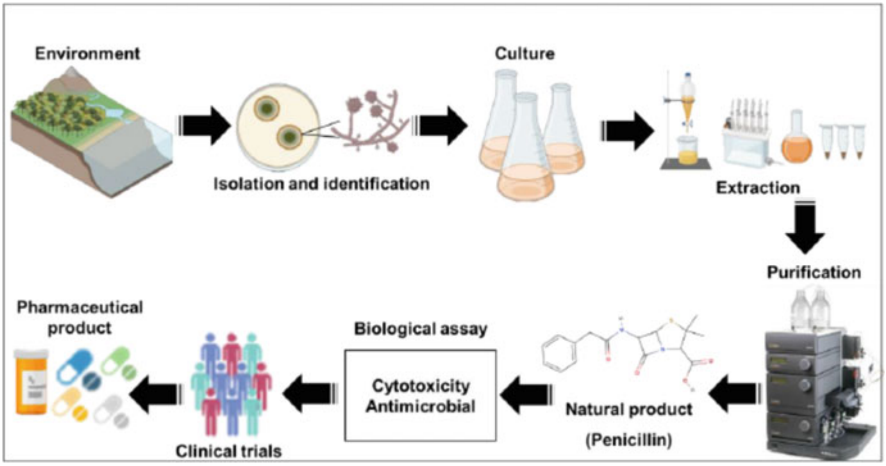


Fig. 14.2 Representation of fungal strain isolation and development of medicines containing natural products as the bioactive component. Penicillin is being used just as an example. Reproduced from Conrado et al. (2022)

product begins with the isolation of the fungus strain from diverse environmental sources (e.g., water, plants, and soil) and the culture of the microorganisms. The product of the culture is processed for extraction and purification of fungi metabolites. Subsequently, biological assays and clinical trials are performed to define the possibility of future pharmaceutical applications of the SM (Fig. 14.2).

However, there are several limitations and drawbacks in this field, such as the handling and isolation of new strains. There are several well-described isolation processes of fungi, including that for endophytes; however, there is some challenge in isolating new fungi species, mainly due to the current techniques applied for the cultivation and strain purification that usually have remained the same in the last years. For obtaining new species, it is mandatory to design new approaches that are able to simulate the condition of the natural habitat from which the microorganisms were isolated. In this aspect, it is essential to overcome challenges related to growing conditions such as pH, temperature, nutrients, and preservation in the laboratory. Fungal culture for obtaining its bioactive metabolites can be performed in either solid-state fermentation (SSF) or submerged fermentation (SmF). The first one, on a solid substrate, can produce a high concentration of metabolites. The SmF occurs in aqueous liquid nutrient media, and it is the most widely used due to the ease of control of fermentation parameters such as pH, temperature, dissolved oxygen, and types of culture media (Conrado et al. 2022).

Also, there is an ongoing search for highly productive fungi for desired compounds followed by their strain improvement through epigenetic modulations, mutations, and genetic engineering to make them suitable for industrial applications. Furthermore, the elucidation of their complete biosynthesis route is more than needed, including all the enzymes and related genes involved through "omics"—

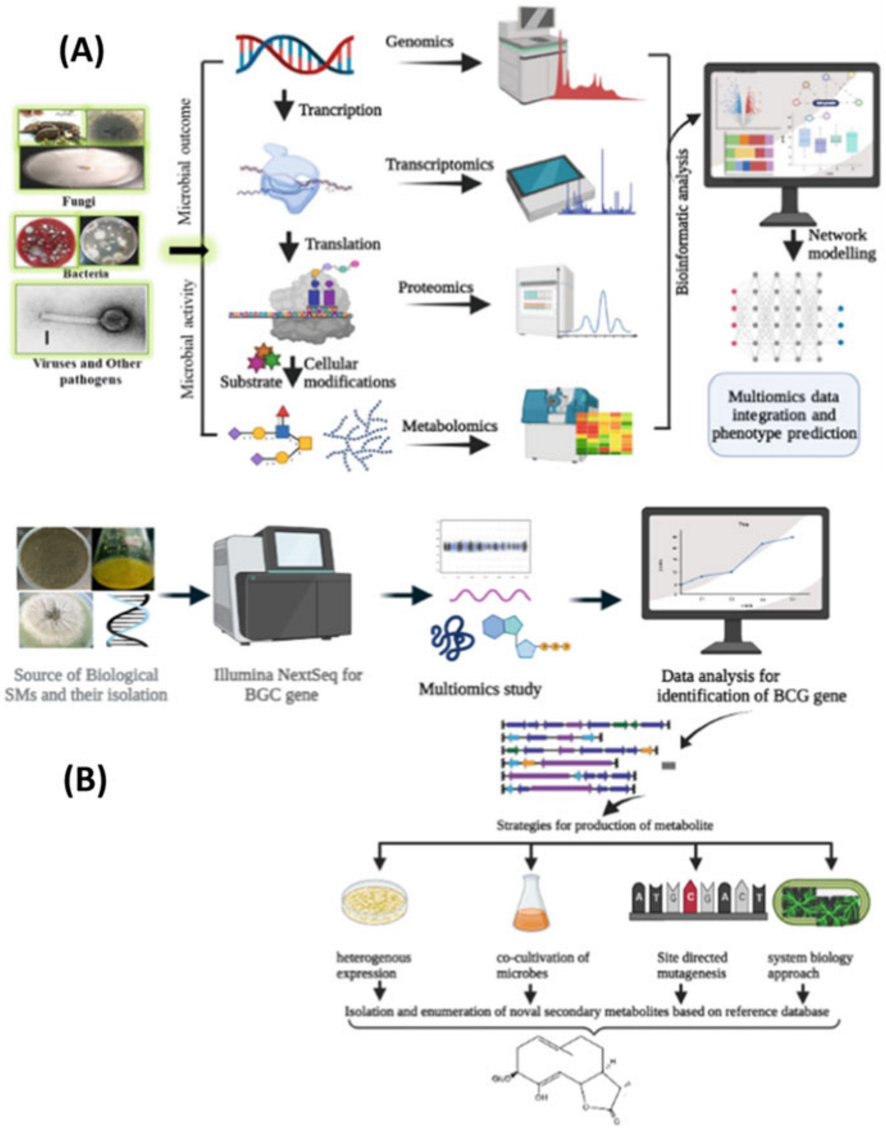


Fig. 14.3 (**a**) Flow chart depicts multi-omic tool with data integration and artificial intelligence modeling used for fungal metabolite studies. (**b**) The use of multi-omics for screening and isolating novel fungal secondary metabolites. Reproduced from Shankar and Sharma (2022)

genomics, transcriptomics, proteomics, and metabolomics—to regulate and manipulate the biosynthesis process for improved productivity (Fig. 14.3). Alternatively, the identified biosynthetic pathway of the bioactive compounds can be assembled and mimicked in convenient systems, offering an approach to produce target compounds with ease (Shankar and Sharma 2022; Singh et al. 2021).

Once the limitations for microorganism isolation, culture, genetic manipulation, and characterization through omics of the biosynthetic route have been overcome, the next step is to proceed with extraction, purification, physicochemical characterization of the SMs, structural elucidation, and metabolomics with multi-omics, along with bioassay techniques for evaluating their bioactivities and structure–activity relationships. In addition, new and advanced omic approaches are needed to screen newer fungi, increase the pool of novel metabolites with their molecular interaction, and exploit the fungal cultures with their metabolic capacity (Fig. 14.3) (Shankar and Sharma 2022). All these processes are very well-described and widely applied in natural product research and have enabled the rapid characterization of valuable novel fungi-derived natural products, which along with cytotoxicity tests and targeted clinical trials have allowed the appropriate design, development, and release in the market of drugs and supplements containing fungi metabolites (Figs. 14.2 and 14.3).

3 Fungi Bioactive Metabolites with Anti-Inflammatory and Antithrombotic Properties as Candidates for the Development of Supplements and Drugs

Within this section, the most important and promising fungi metabolites with anti-inflammatory and antithrombotic potential that are/can be used for the development of supplements and drugs against inflammation-related disorders are presented. These are fungi-derived vitamins, carotenoid-colored metabolites, phenolic compounds/pigments, lipid bioactives, alkaloids, terpenes, polyketides, and several other bioactive fungi metabolites, which possess various biological activities including anticancer, anti-inflammatory, antithrombotic, antimicrobial, and antioxidant potential against chronic disorders.

3.1 Fungi-Derived Vitamins and Bioactive Carotenoid-Based Colored Pigments

Micronutrients known as vitamins are crucial for sustaining the body's normal physiological functions and are required in small quantities. As mammals are unable to produce these essential nutrients, it is imperative to obtain them through dietary supplementation from external sources to ensure balanced metabolism in all living organisms (Shimizu 2001; Gupta and Gupta 2015). Certain vitamins act as coenzymes that assist in the biochemical reactions catalyzed by enzymes. For example, vitamin K is essential for normal blood clotting and plays a vital role in activating receptors that facilitate transcription mechanisms in bone tissues, making it a valuable treatment option for osteoporosis (Berg et al. 2002; Bolander 1997). The

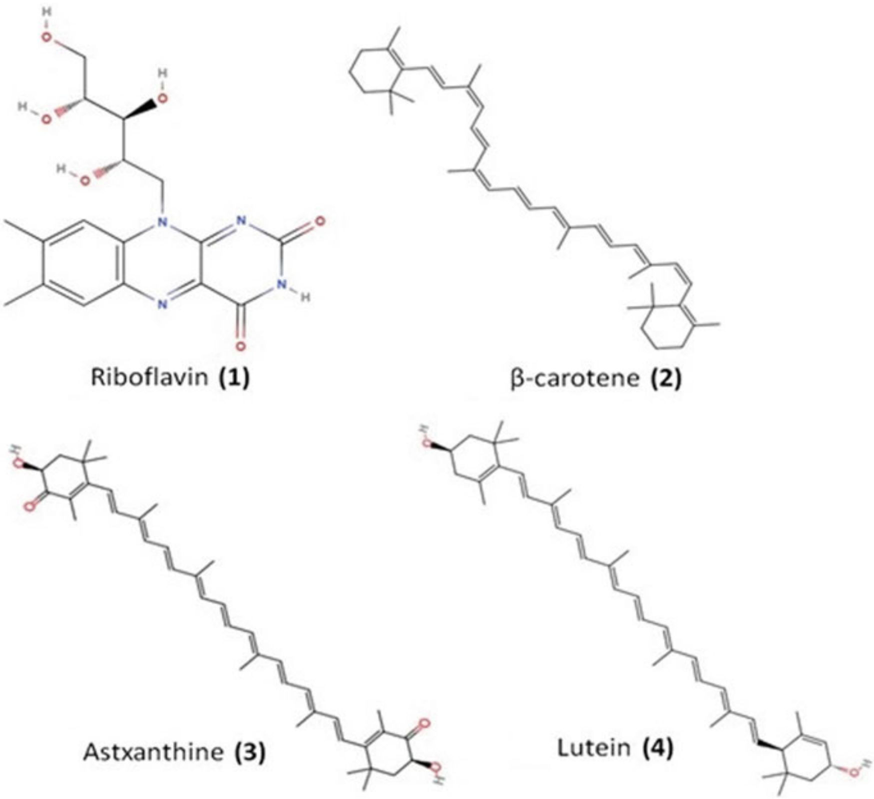


Fig. 14.4 Chemical structures of natural fungi vitamins and bioactive carotenoid pigments with anti-inflammatory potential. Structures were obtained from https://molview.org/ (accessed on April 2, 2023)

presence of vitamin A is necessary as a precursor to rhodopsin and other visual pigments, and it also plays a role in activating specific gene transcription processes that aid in growth and development (Berg et al. 2002). Microorganisms, such as fungi, naturally produce vitamins during regular metabolism, which are commonly used as food additives, health supplements, and therapeutic agents (Singh et al. 2017). To commercially produce fungi-derived vitamins, suitable fungi can be utilized in direct fermentation or through a combination of chemical and microbiological processes (Shimizu 2001; Bhalla et al. 2007). Characteristic examples of industrial production of vitamins from several fungi species are riboflavin (**1**) and β-carotene (**2**) (Fig. 14.4) (Bhalla et al. 2007; Demain 1999; Survase et al. 2006; FAO/WHO. 2001; Wang et al. 2012a; Mata-Gómez et al. 2014).

Vitamin B2, also known as riboflavin, is a water-soluble vitamin that is necessary for growth and reproduction. A lack of this essential vitamin can lead to cheilosis and dermatitis in humans. *Eremothecium ashbyii* and *Ashbya gossypii*, which are closely related ascomycetes, are commonly utilized microorganisms for the fermentative production of riboflavin (Demain 1999; Survase et al. 2006). Of the two, *A. gossypii* is the preferred choice due to its remarkable efficiency in producing riboflavin. It can generate up to 40,000 times the amount of vitamin necessary for its own growth (Survase et al. 2006).

Provitamin A, called β-carotene, is necessary for healthy growth, reproduction, and vision. Night blindness, changes in the skin, and mucosal membranes are all brought on by a vitamin A deficiency or malabsorption (FAO/WHO. 2001). The formation of β-carotene involves the fungi *Blakeslea trispora*, *Phycomyces blakesleeanus*, *Mucor circinelloides*, *Rhodotorula* spp., and *Choanephora cucurbitarum*. Due to their high yield of β-carotene, *Blakeslea trispora* and *Phycomyces blakesleeanus* are chosen and employed for submerged fermentation in industrial production (Wang et al. 2012a; Mata-Gómez et al. 2014).

Carotenoid-based bioactive pigments have been found in a variety of fungi, primarily those found in marine habitats, while engineered fungi such as yeasts can also be used for their production in industrial scale (Elbandy 2022; Galasso et al. 2017; Elbandy et al. 2009; Takahashi et al. 2020). Even though microalgae are the primary source of carotenoids used in industry, however, alternative organisms like fungi may be of use in other fields such as the cosmetics or pharmaceutical industries (Ambati et al. 2014; Maoka 2011; Corinaldesi et al. 2017). Thus, while the focus of carotenoid production has been on algal sources, marine fungi and pigmented yeasts can also be used for de novo synthesis of such biomolecules (Corinaldesi et al. 2017).

More specifically, several carotenoids are synthesized by various yeast species that have been isolated from the marine environment. Notably, the genera *Xanthophyllomyces*, *Rhodotorula*, and *Phaffia* have been utilized to produce one of the most bioactive carotenoids used in supplements, astaxanthin (**3**) (Fig. 14.4) (Ambati et al. 2014). Despite yeasts and bacteria yielding smaller quantities of astaxanthin compared to algae, they have the advantage of quicker rates of growth and more straightforward cultivation techniques (Mata-Gómez et al. 2014; Bumbak et al. 2011). Marine organisms, notably fungi and prokaryotes, exhibit tremendous potential for the creation and commercialization of novel antioxidant compounds and carotenoids, which can be used in a variety of industries (Corinaldesi et al. 2017). Marine carotenoids offer numerous advantages due to their potent antioxidant, repairing, antiproliferative, and anti-inflammatory properties. They can be employed to provide skin photoprotection against the detrimental impact of solar UV radiation or as nutraceutical/cosmeceutical components to safeguard against oxidative stress-induced diseases (Nichols and Katiyar 2010; Berthon et al. 2017; Gonzalez et al. 2011).

Fungi-derived α- and β-carotene (**2**), lutein (**4**), and astaxanthin (**3**) are examples of exogenous antioxidants that are crucial in preventing oxidative damage caused by free radicals via their scavenging activity (Birben et al. 2012; D'Orazio et al. 2012). These compounds have lipophilic properties, which allow them to act as a natural defense for both marine and earth-bound plants by crossing the cellular membrane. Their ability to cross the blood–brain barrier allows them to be biologically active in organs such as the brain (Elbandy 2022).

Di Tomo et al. (2012) found that the addition of carotene and lycopene was able to reduce TNF-α induced inflammatory response in human umbilical vein endothelial cells (HUVECs). These antioxidant molecules inhibited monocyte (U937)–endothelial adhesion while also limiting gene expression of the vascular adhesion proteins, VCAM-1, ICAM-1, and E-selectin. Lycopene and β-carotene helped sustain nitric oxide (NO) bioavailability resulting in control of the cellular redox environment (Di Pietro et al. 2016; Bian et al. 2023).

Lutein (**4**) is another carotenoid with strong antioxidant capacity and an important component of macular pigment in the retina, and thus, it possesses wide applications in pharmaceutical, food, feed, and cosmetics industries. Besides extraction from plant and algae, microbial fermentation using engineered cell factories of fungi (mostly engineered yeasts, such as *Saccharomyces cerevisiae*) to produce lutein has emerged as a promising route (Bian et al. 2023). Dwyer et al. (2001) research, comprising in vitro, in vivo, and epidemiological studies, demonstrates lutein's potential as a protective agent against the early stages of atherosclerosis (Dwyer et al. 2001). Their co-culture model of lipoprotein oxidation with the artery wall revealed a significant dose-dependent reduction in the chemotactic signal for monocytes in the presence of lutein (0.1, 1, 10, and 100 nM), resulting in the inhibition of monocyte inflammation associated with LDL in the artery wall. This effect was observed in both apoE-null and LDL receptor-null mice, wherein an enriched lutein diet led to a significant reduction in atherosclerotic lesion size in the aortic arch. Furthermore, high plasma lutein levels were correlated with the progression of intima-media thickness (Dwyer et al. 2001).

The red pigment astaxanthin (**3**) can inhibit peroxidation by the protection of lipid bilayers from free radicals. The scavenging properties of this marine fungi carotenoid are associated with the molecular structure (Fig. 14.6), which is thought to be responsible for its 10 times higher antioxidant activity compared to previously mentioned carotenoids like β-carotene and lutein (Galasso et al. 2017; Gammone et al. 2015).

Astaxanthin was also found to reduce COX-2 expression-related neuroinflammation (Si and Zhu 2022). Endothelial function was improved in resistance arteries with astaxanthin enriched diet in hypertensive rats (Monroy-Ruiz et al. 2011). In addition to this effect, a decrease in oxidative stress was also observed and an improvement in NO bioavailability. 10 μM of astaxanthin was able to reduce pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, previously induced by the treatment with 100 μM of H_2O_2 (Galasso et al. 2017; Si and Zhu 2022).

It has also been proposed that astaxanthin's anti-inflammatory and anti-apoptotic effects in the neural system are also related to elevated myelin basic protein (MBP) expression and decreased levels of caspase-3, iNOS, granulocyte colony-stimulating factor, and growth-related oncogene (Elbandy 2022; Aslankoc et al. 2022). Furthermore, astaxanthin decreased microglial activation and the expression of various pro-inflammatory cytokines, which further resulted in the suppression of neuroinflammation. The anti-inflammatory activity of astaxanthin was demonstrated by the nuclear translocation of NFκB p65, as well as by the suppression of p38 and Erk1/2 phosphorylation (Elbandy 2022; Pietrasik et al. 2022; Zhao et al. 2021).

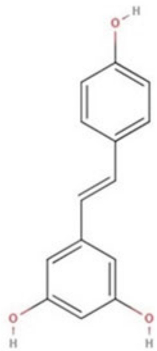
3.2 Fungi-Derived Classic and Complex Bioactive Phenolic Compounds/Pigments with Anti-Inflammatory and Antithrombotic Properties

Several fungi produce a plethora of phenolic compounds, phenylpropanoids and aromatic amino acids. Such secondary metabolites consist of phenolic compounds and are secreted from the fungal metabolic pathways and/or the plant metabolic pathway (of plants that symbiote with endophyte fungi), which is called the shikimate pathway. Metabolites of this group include compounds like folic acid and salicylic acid, which help in reducing inflammation and pain, while they also produce the antioxidant drug resveratrol (**5**) (Fig. 14.5) (Singh et al. 2017, 2021). Phenolic compounds have many functions, while due to the high antioxidant effect and free radical scavenging property, phenylpropanoid compounds have major attention in the area of human health, and nowadays, their functions are updated by the use of multi-omic tools (Singh et al. 2017, 2021; Shankar and Sharma 2022).

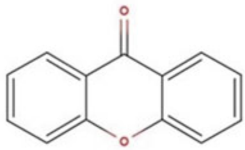
Resveratrol (*trans*-3,5,4′-trihydroxystilbene) is the most well-established polyphenol used as drug and is found mostly in grapes, berries, and fermented alcoholic beverages like wine, where *S. cerevisiae* is used as the main yeast for the fermentation, but can also be made by some fungi. It is a phytoalexin, i.e., a low molecular weight secondary metabolite. *Alternaria* sp. 61, isolated from Merlot cobs, can also produce resveratrol, as well as recombinant *S. cerevisiae* upon feeding of coumaric acid or L-tyrosine (Sanchez and Demain 2017; Shi et al. 2012; Shin et al. 2012). Resveratrol has exhibited potent antioxidant and anti-inflammatory activities, as well as anti-platelet aggregation and anti-atherogenic properties, and thus, it possesses beneficial effects against inflammation, carcinogenesis, oxidation, aging, diabetes, and renal and neurodegenerative disease (Tsoupras et al. 2007, 2009; Fragopoulou et al. 2004; Sanchez and Demain 2017; Sánchez-Fidalgo et al. 2010). Moreover, resveratrol was also found to reduce the levels of the potent inflammatory mediator and platelet-activating factor (PAF) by inhibiting its synthesis and thus reducing the inflammatory status (Tsoupras et al. 2007, 2009). Such bioactive phenolic compounds from fungi like resveratrol, which can reduce the levels and/or inhibit the activities of thrombo-inflammatory mediators like PAF and thrombin, may potentially reduce the risk of developing chronic disorders (Tsoupras et al. 2018, 2009, 2022a).

Moreover, a phenolic fraction derived from the HPLC separation of a bioactive extract from *B. bassiana* exhibited potent anti-inflammatory and antithrombotic activities against PAF in rabbit platelets (Tsoupras et al. 2022b). However, more studies are needed in order to elucidate the bioactive phenolic molecules that can be derived from such entomopathogenic fungus.

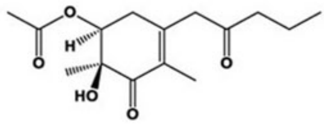
A mushroom species with high functional and nutraceutical potential of high market value is *Agaricus subrufescens* (synonymy *Agaricus blazei* and *Agaricus brasiliensis*). It is commercialized in several countries such as Brazil (brand name "Sun mushroom"), China (Ji Song Rong), and Japan (Himematsutake). Sun mushroom contains polyphenols and polysaccharides and is known to decrease oxidative



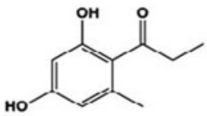
Resveratrol **(5)**



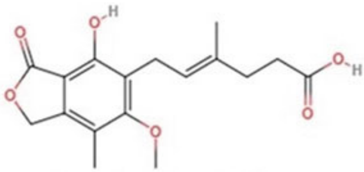
Xanthone **(6)**



Azaphylone monapurpureusone **(7)**



Monapurpureusin (8)



Mycophenolic acid **(9)**

Fig. 14.5 Chemical structures of fungi bioactive phenolic compounds/pigments with anti-inflammatory potential. Most of the structures were obtained from https://molview.org/ (accessed on April 2, 2023), while (**7**) and (**8**) were reproduced from Takahashi et al. (2020)

stress and prevent non-transmitted chronic disorders (NTCD); it is indicated to have antioxidant, antitumor, anti-inflammatory, and immunomodulatory properties (Shankar and Sharma 2022; Takahashi et al. 2020; Navegantes-Lima et al. 2020).

For example, *Agaricus brasiliensis* extract rich in polyphenols showed anti-inflammatory, immunomodulatory, and antioxidant effects in the cecal ligation and puncture (CLP) sepsis model (Navegantes-Lima et al. 2020). More specifically, the aqueous extract of *A. brasiliensis* reduced systemic inflammatory response and improved bacteria clearance and mice survival. In addition, *A. brasiliensis* decreased the oxidative stress markers in serum, peritoneal cavity, heart, and liver of septic animals, as well as ROS production (in vitro and in vivo) and *tert*-butyl hydroperoxide-induced DNA damage in peripheral blood mononuclear cells from healthy donors in vitro. In conclusion, the aqueous extract of *A. brasiliensis* was able to increase the survival of septic animals by a mechanism involving anti-inflammatory, immunomodulatory, and antioxidant protective effects (Navegantes-Lima et al. 2020).

Xanthone (**6**) (Fig. 14.5) is the basis of several xanthones, including fungi-derived xanthones, which are another class of bioactive phenolic compounds showing antioxidant and anti-inflammatory properties and potential medicinal benefits (Feng et al. 2020). For example, the anti-neuroinflammatory assay of Hypoxylon xanthone A from soil fungus *Hypoxylon* sp., as manifested by the inhibitory effect on LPS-induced NO production in BV-2 microglial cells, indicated almost the same inhibitory effect as the antibiotic minocycline in a dose-dependent manner within the concentration of 1–50 μM, suggesting that hypoxylon xanthone A could be a new potential neuroinflammation inhibitor (Takahashi et al. 2020; Xiao et al. 2020).

Another example to enhance the quantity of easily available phenolic pigments from fungi is engineered *Monascus* species by subjecting them to mutations. One of these mutant strains of *M. purpureus* was grown in fermented rice extract, leading to the production of two new compounds—the azaphylone monapurpureusone (**7**) and the brownish natural product monapurpureusin (**8**) (Fig. 14.5). These compounds and their derivatives produced by reactions with other biomolecules (i.e., the water-soluble red pigments monascorubramine and rubropunctatin) have exhibited remarkable superoxide radical scavenging activity, either comparable to or surpassing the control gallic acid, and superior anti-inflammatory activity in comparison with the control quercetin (Wu et al. 2019). In general, *Monascus* pigments come in 54 different varieties. They have a remarkable range of functions, including antibacterial, anticancer, antimutagenesis, antidiabetes, anti-obesity, anti-inflammatory, cholesterol-lowering, immunosuppressive, and hypotensive (Sanchez and Demain 2017; Feng et al. 2012; Lee and Pan 2012).

Some classic and/or more complex fungi phenolic molecules can reduce the inflammatory response indirectly as immunosuppressants. For example, mycophenolic acid (**9**) is a mesoterpenoid with a phenolic functional group, synthesized by the fungi *Penicillium brevicompactum*, *Penicillium stoloniferum*, and *P. echinulatum*, with a primary use as an immunosuppressive drug and especially to prevent organ transplant rejection. It reversibly inhibits inosine monophosphate dehydrogenase, the enzyme that controls the rate of synthesis of guanine monophosphate in the de novo pathway of purine synthesis used in the proliferation of B and T lymphocytes, which concludes to immunosuppressant and reduced inflammatory response (Patel et al. 2017; Anderson et al. 1988; Bills and Gloer 2016).

3.3 Fungi Lipid Bioactives with Anti-Inflammatory and Antithrombotic Properties

3.3.1 Fungi-Derived Anti-Inflammatory and Antithrombotic Fatty Acids

Fungi produce several unsaturated fatty acids, in a combination that usually has anti-inflammatory potential (Fig. 14.6). For example, almost all fungi contain the monounsaturated fatty acid (MUFA) oleic acid (OA; 18:1 omega 9) (**10**), which has shown strong anti-inflammatory and antithrombotic properties against several inflammatory mediators, including PAF (Nunez et al. 1990). In addition, various fungi produce also several of the long-chain polyunsaturated fatty acids (PUFA), such as gamma linoleic acid (GLA; 18:3 omega-6) and alpha-linolenic acid (ALA; 18:3 omega-3) (**11**) and (**12**) (i.e., from *Mucor circinelloides)*, arachidonic acid (ARA; 20:4 omega-

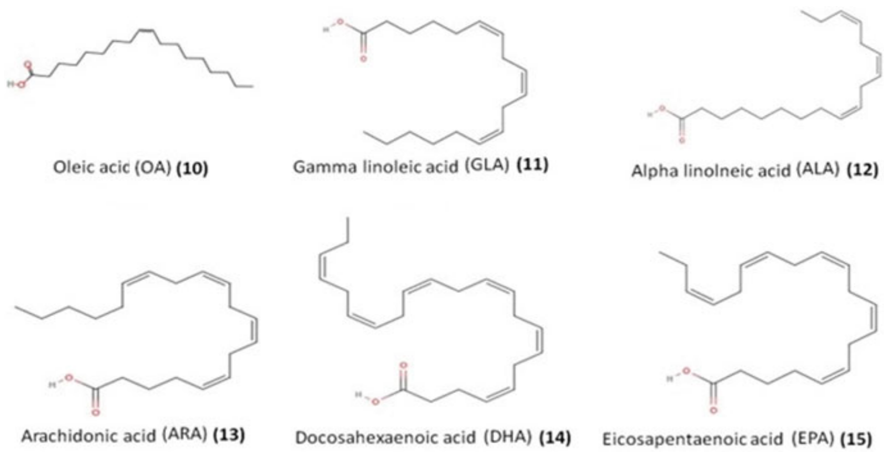


Fig. 14.6 Chemical structures of fungi bioactive unsaturated fatty acids with anti-inflammatory potential. Structures were obtained from https://molview.org/ (accessed on April 2, 2023)

6) (**13**) (i.e., from *Mortierella alpine)*, docosahexaenoic acid (DHA; 22:6 omega-3) (**14**) (i.e., from *Crypthecodinium cohnii spp.)*, and eicosapentaenoic acid (EPA; 20:5 omega-3) (**15**) (i.e., from genetically modified *Y. lipolytica*. The oil produced from fungi has much higher levels of EPA than natural oils. EPA is important for the anti-inflammatory activity of fish oils, thus contributing to cardiovascular and joint health (Tsoupras et al. 2022a; Sanchez and Demain 2017). Consumption of such PUFA-containing oily products with a low ratio of omega-6/omega-3 PUFA promotes an anti-inflammatory potential since diets and foods containing such a ratio have been found to possess strong anti-inflammatory health benefits against several inflammation-related disorders (Simopoulos 2008). PUFAS are the principal component of cell membrane phospholipids and thus are used heavily in the infant formula industries (especially ARA and DHA). EPA and DHA can be utilized to avoid heart issues. They control cell fluidity, the attachment of certain enzymes to cell membranes, and the transmission of signals and other metabolic activities. They are involved in the manufacture of eicosanoids, leukotrienes, prostaglandins, and resolvins, which have anti-inflammatory, anti-arrhythmic, and anti-aggregatory properties. Several of them promote cardiovascular health, and others increase visual function and cognition in newborns and adults (Sanchez and Demain 2017).

3.3.2 Polar Lipids

Polar lipids are important biomolecules and structural elements for all cells in nature, with a plethora of diverse bioactivities. Polar lipids are amphiphilic molecules that generally have two fatty acids esterified to a glycerol- or a sphingosine-based backbone and a phosphorus functional group for phospholipids or a sugar for glycolipids that is linked to a head group (Fig. 14.7a). Lately, it has been found

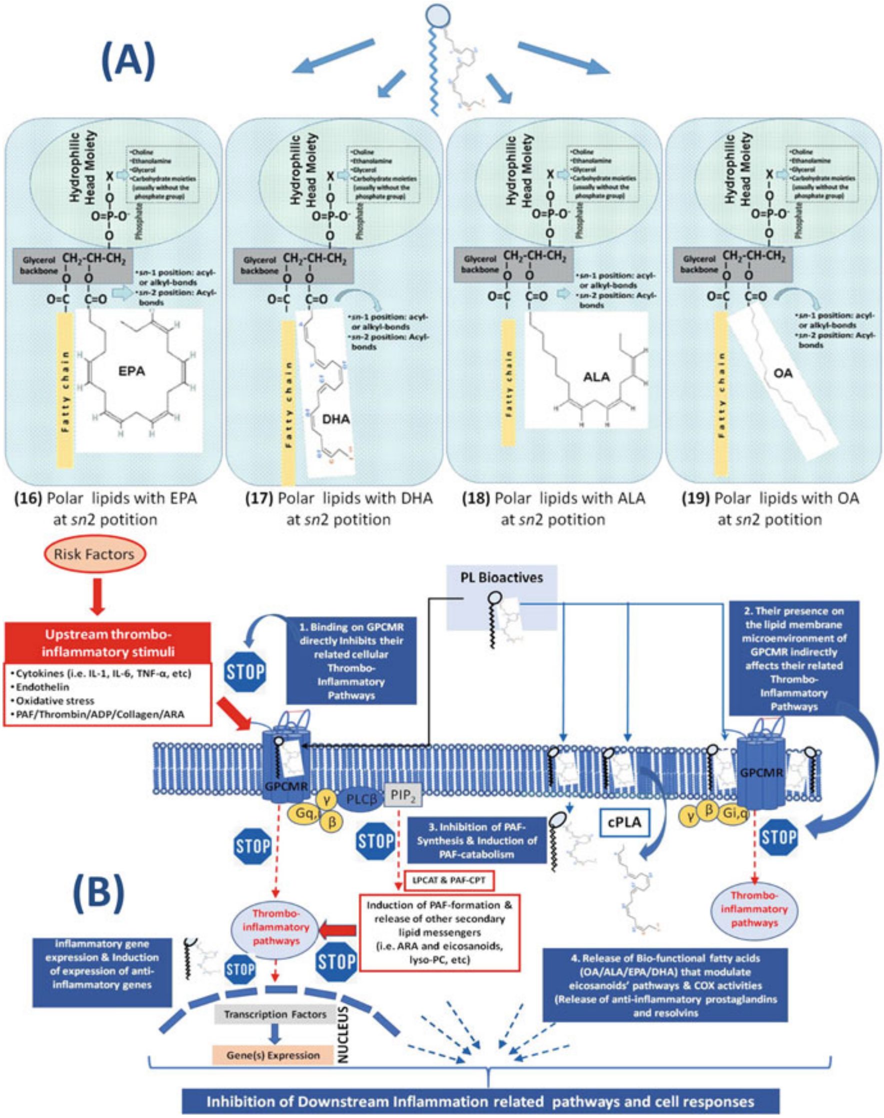


Fig. 14.7 Structures (**a**) and mechanisms of action (**b**) of classic bioactive polar lipids with anti-inflammatory and antithrombotic properties; (**a**) bioactive polar lipids with unsaturated fatty acids at their *sn*2 position of their glycerol backbone. *EPA* eicosapentaenoic acid (C20:5 omega-3), *DHA* docosahexaenoic acid (C22:6 omega-3), *ALA* alpha-linolenic acid (C18:3 omega-3), *OA* oleic acid (C18:1 omega-9). (**b**) Modes of beneficial actions of bioactive polar lipids (in blue color) against the thrombo-inflammatory related pathways and cell responses (red color). *PL* polar lipids, *PAF* platelet-activating factor, *ADP* adenosine 5′ diphosphate, *GPCMR* G-protein-coupled membrane receptors, *cPLA2* cytoplasmic phospholipase A2, *LPCAT and PAF-CPT* basic regulatory biosynthetic enzymes of PAF, *ARA* arachidonic acid, *COX* cyclooxygenase. Reproduced with modifications from Tsoupras et al. (2022a)

that bioactive polar lipids with unsaturated fatty acids in their structures (usually at the *sn*2 position), such as polar lipids with EPA (**16**), polar lipids with DHA (**17**), polar lipids with ALA (**18**), and polar lipids with OA (**19**) (Fig. 14.7a), possess higher bioavailability of their unsaturated fatty acids throughout the body, due to their amphiphilic properties, while most importantly they possess strong anti-inflammatory and antithrombotic properties against several mediators and inflammatory pathways, by a variety of mechanisms of actions (Fig. 14.7b), with promising health benefits against atherosclerosis and CVD, cancer and metastatic procedures, renal and neurodegenerative disorders, persistent infections and associated inflammatory manifestations, allergy and asthma, sepsis, etc. (Tsoupras et al. 2018, 2022a).

For example, such bioactive polar lipids have modulated or even reduced the formation of arteriosclerotic plaques, by reducing the levels of the inflammatory and thrombotic mediator, PAF, and its atherogenic effects. Apart from modulating PAF metabolism toward reduced PAF levels, such fungi-derived bioactive polar lipids have also inhibited the inflammatory and thrombotic pathways of both PAF and thrombin, while they have reduced the platelet activation and aggregation induced by well-established platelet agonists, collagen, and ADP (Moran et al. 2021; Fragopoulou et al. 2004; Tsoupras et al. 2022b). More specifically, it has recently been found that several yeasts used for the production of fermented foods and beverages (Moran et al. 2021; Fragopoulou et al. 2004) and fungi of bio-agro/food technological applications like those used as natural entomopathogenic agents for organic cultures, such as *Beauveria bassiana* (Tsoupras et al. 2022b), contain such bioactive polar lipids with strong anti-inflammatory and antithrombotic properties against the thrombo-inflammatory mediators, PAF and thrombin, and against the well-established platelet agonists, collagen, and ADP (Moran et al. 2021; Fragopoulou et al. 2004; Tsoupras et al. 2022b).

It seems that the anti-inflammatory and antithrombotic anti-PAF properties of these fungi-derived polar lipid bioactives occur either through affecting beneficially PAF metabolism toward reduction in its levels of homeostatic ones and/or through inhibiting the binding of PAF on its receptor and thus inhibiting PAF-related inflammatory and thrombotic pathways and activities (Fig. 14.7b) and subsequently reducing the risk for PAF-associated inflammatory chronic disorders such as atherosclerosis, CVD, and cancer (Tsoupras et al. 2018, 2009, 2022a). Moreover, apart from the strong anti-inflammatory and antithrombotic properties of the whole structures of such bioactive polar lipids, it has also been proposed that once the rich in unsaturated polar lipids have surpassed the intestine barrier and are bound to and transferred from plasma lipoproteins to the cell membranes of all tissues, there a cytoplasmic phospholipase A2 (PLA2) releases their unsaturated fatty acids from their structure of these membrane-bound polar lipids, while the released unsaturated fatty acids interacts with the eicosanoids pathways (COX-enzymes) for reducing and resolving inflammation and the inflammatory cell-response (Fig. 14.7b).

3.3.3 Other Fungi-Derived Lipid Bioactives with Anti-Inflammatory and Antithrombotic Properties

Several other fungi-derived lipid bioactives have also been found to possess anti-inflammatory and antithrombotic potential. For example, ergosterol (**20**) (Fig. 14.8), the main sterol present in various fungal membrane cells, has a range of activities including cell cycle control, regulation, and permeability, as well as several health-promoting effects such as, anti-inflammatory, antioxidant, anticancer, and anti-hypercholesteremic (Rousta et al. 2023). Ergosterol is also implicated in the synthesis of vitamin D2 (ergocalciferol) by conversion of ergosterol by UV radiation. This form of vitamin D2 is converted to calcitriol, the biologically active form of vitamin D by the body. Vitamin D is an important vitamin for the prevention of various metabolic diseases like hypertension, diabetes, and cancer (Feng et al. 2020). Deficiency of vitamin D has been associated with COVID-19 mortality (Tsoupras et al. 2020a, b; Zabetakis et al. 2020).

Vitamin D and its analogs like paricalcitol have also exhibited strong anti-inflammatory and antithrombotic properties by inhibiting the inflammatory actions of PAF in vitro in platelets, they reduced PAF synthesis in vitro in cell cultures of mesangial cells, while in an in vivo trial daily administration of paricalcitol in hemodialysis patients for a month resulted also in modulation of PAF metabolism toward reduced PAF synthesis and increased PAF catabolism and thus toward reduced PAF levels in their blood, which subsequently resulted in reduced levels

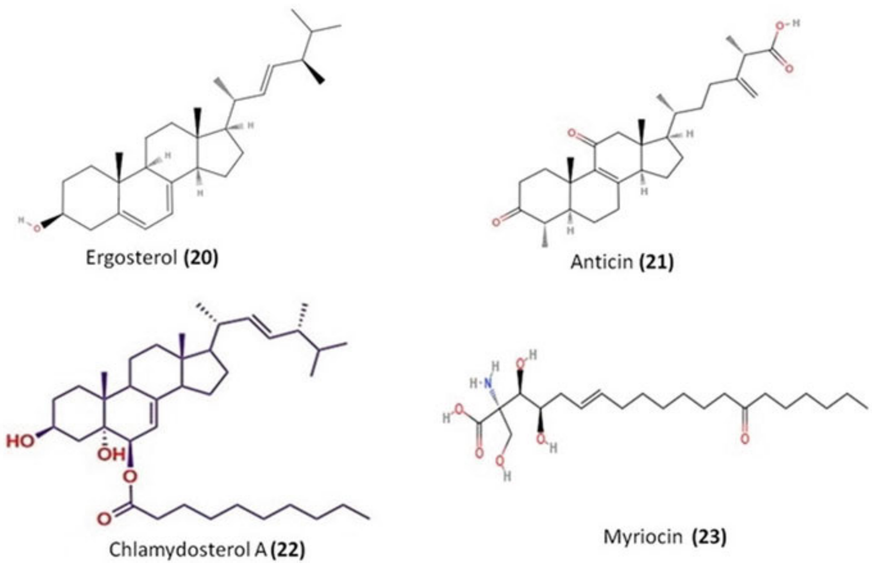


Fig. 14.8 Chemical structures of other fungi lipid bioactives with anti-inflammatory potential. Structures of (**20**), (**21**), and (**23**) molecules were obtained from https://molview.org/ (accessed on April 2, 2023), while (**22**) was reproduced from Al-Rabia et al. (2021)

of other inflammatory cytokines and a beneficial decrease in the inflammatory status in the blood of these patients versus control subjects (Verouti et al. 2013). Since the rich diet source of vitamin D is animal products, the fungi as the only vegetarian source of vitamin D are highly considered.

Another class of fungi-derived bioactive lipid compounds of increasing prominence found in edible mushrooms includes antcins (**21**) (Fig. 14.8) and steroids that contain an ergostane-type skeleton and are produced by *Antrodia* species such as *Antrodia cinnamomea* and *Antrodia salmonea* (Takahashi et al. 2020). Studies suggest that these compounds are promising agents in the treatment of cancer, inflammation, diabetes, and diseases resulting from oxidative stress (Takahashi et al. 2020). A study tracking 36,499 middle-aged and elderly Japanese men over an average of 13.2 years found a positive relationship between regular mushroom consumption and decreased incidence of prostate cancer (Zhang et al. 2020).

Two other ergosterol derivatives namely chlamydosterols A (**22**) (Fig. 14.8) [(22*E*,24*R*)-ergosta-7,22-diene-3β,5$^{\alpha}$,6β-triol 6-decanoate] and ergosta-5,7,22-triene-3β-ol, from the EtOAc extract of the endophytic fungus *Fusarium chlamydosporum* isolated from *Anvillea garcinia* (Asteraceae) leaves growing in Saudi Arabia, showed a 5-lipoxygenase (5-LOX) inhibitory potential compared to a classic 5-LOX inhibitor, indomethacin (Al-Rabia et al. 2021).

Some classic and/or more complex fungi lipid molecules can reduce the inflammatory response indirectly as immunosuppressants. For example, myriocin (ISP-I) (**23**) (Fig. 14.8) is an amino acid lipid produced by the fungus *Isaria sinclairii*, whose structural model is used as a template for the synthesis of fingolimod, commercially available as Gilenya. Used in the treatment of multiple sclerosis through the activation of its structure, this drug connects with extracellular G protein-coupled receptors, preventing the release of lymphocytes that enter the central nervous system and thus indirectly prevent the neuroinflammatory response of sclerosis (Fujita et al. 2000).

3.4 Alkaloids

Alkaloids are an important group of nitrogen-containing secondary metabolites, such as caffeine, cocaine, nicotine, morphine, and strychnine, which consist of one or more nitrogen atoms within their heterocyclic ring. Alkaloids have several biological activities including anti-inflammatory properties (Mehta et al. 2022; Debnath et al. 2018). For example, the addition of pyrrole alkaloid into the cell of fungus *Curvularia* sp. IFB-Z10, associated with white croaker, induces the generation of an anti-inflammatory metabolite named curindolizine (**24**) (Fig. 14.9) (Mehta et al. 2022; Han et al. 2016). In general, several species of *Curvularia* are known to synthesize various bioactive alkaloid compounds including curvulamine, curindolizine, and curvupallides, which show antimicrobial and anti-inflammatory activities (Mehta et al. 2022). Moreover, marine fungi-derived indole alkaloids are also very promising and an active group of molecules. They possess various

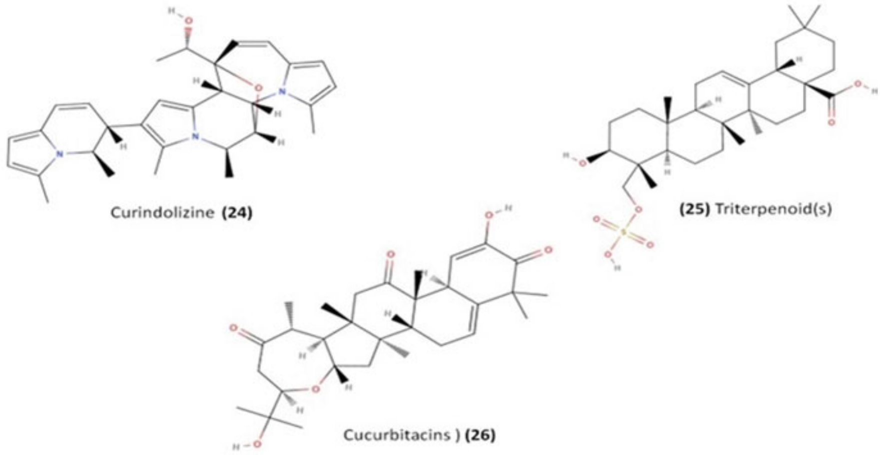


Fig. 14.9 Chemical structures of characteristic fungi-derived alkaloids and terpenoids with anti-inflammatory potential. Structures were obtained from https://molview.org/ (accessed on April 2, 2023)

biological activities like antiparasitic, cytotoxic, serotonin and antagonistic realms, anti-inflammatory, and antiviral (Shankar and Sharma 2022; Gul and Hamann 2005).

3.5 Terpenoids

Terpenes are a major class of bioactive metabolites that are produced from a higher class of Polyporales group of basidiomycetes. These compounds are structural constituents of another group of metabolites that are formed through the linkage of isoprene units. Different NMR and other omic tools confirm the member of the terpenoid class of compounds such as steroids, menthol, and taxol, which have key components for anticancer drugs and β-carotene properties. These bioactive compounds possess anti-inflammatory properties and anti-infection, anticancer, antiproliferative, and antiangiogenic medicinal benefits (Shankar and Sharma 2022). Mushroom secondary metabolites triterpenes (**25**) (Fig. 14.9), abundant in reishi mushroom (*Ganoderma lucidum*), inhibit various pro-inflammatory mediators, such as TNF-α, interleukin-6, nitrogen monoxide free radical, prostaglandin E, nuclear factor-kappa B (NF-κB), and cyclooxygenase-2 (COX-2), while *Poria cocos* mushroom incorporates lanostane triterpenoids (**25**) (Fig. 14.9) that improve inflammation and treat tumors (Bell et al. 2022). Cucurbitacins (**26**) (Fig. 14.9) belong to cucurbitane-type tetracyclic triterpenoid saponins that are abundant in several natural sources, while they are also present in some fungi. Several studies have shown that cucurbitacins have significant biological activities, such as anti-inflammatory, antioxidant, antimalarial, antimicrobial, hepatoprotective, and antitumor potential (Varela et al. 2022).

3.6 Other Fungi Metabolites with Well-Established Pharmaceutical Health Benefits That Also Exhibit Anti-Inflammatory Effects

A plethora of well-established pharmaceutical compounds have been derived from several fungi species. These compounds have been used against specific pathological conditions with high specificity and pharmacological actions. Nevertheless, there are a lot of studies lately indicating the potential pleiotropic effects of several of these drugs. Thus, apart from their classic pharmaceutical actions, the newly observed pleiotropic effects and multifunctional applications of these compounds, and especially their potential anti-inflammatory and antithrombotic properties, may provide additional perspectives for the appropriate choice of a drug/drug combination against a specific inflammation-related condition where anti-inflammatory actions will provide further health benefits by reducing the inflammatory burden. Characteristic examples of such fungi-derived metabolites and their derivatives that are used as several drugs and also possess pleiotropic effects, including anti-inflammatory potency, are further analyzed below.

3.6.1 Drugs Containing Fungal Polyketides and Their Derivatives with Anti-Inflammatory Potential

Fungal polyketides are common metabolites present in large groups of ascomycete and basidiomycete fungi. All groups of microbial polyketides are synthesized by multi-domain polyketide synthases (PKSs), which are structurally diverse. These secondary metabolites contain also a fatty group and are formed through the acetate pathway within the cell by coupling of acetate groups. In the fatty acid group, crude fat is considered under all categories of lipid compounds, including fatty acids, monoglycerides, diglycerides, triglycerides, sterols, and phospholipids. These groups of metabolites include antibiotics, statins (lowers cholesterol levels), and antidepressant drugs. Characteristic pharmaceutically modified polyketides that are used as drugs are the cholesterol-lowering statin, lovastatin (**27**) (Fig. 14.10), and the anti-mycotic drug griseofulvin (**28**) (Shankar and Sharma (2022).

Statins are one of the most well-established cholesterol-lowering drugs used for the prevention and treatment of cardiovascular disorders. In 1976, Akira Endo at the Sankyo Company, Tokyo, identified the first inhibitor of the HMG-CoA reductase, which drives down the levels of intracellular cholesterol, thereby embarking on the long journey of evolution of statin drugs (Sultan et al. 2019). Several statins are fungi metabolites, such as lovastatin, a bioactive polyketide commercially sold as

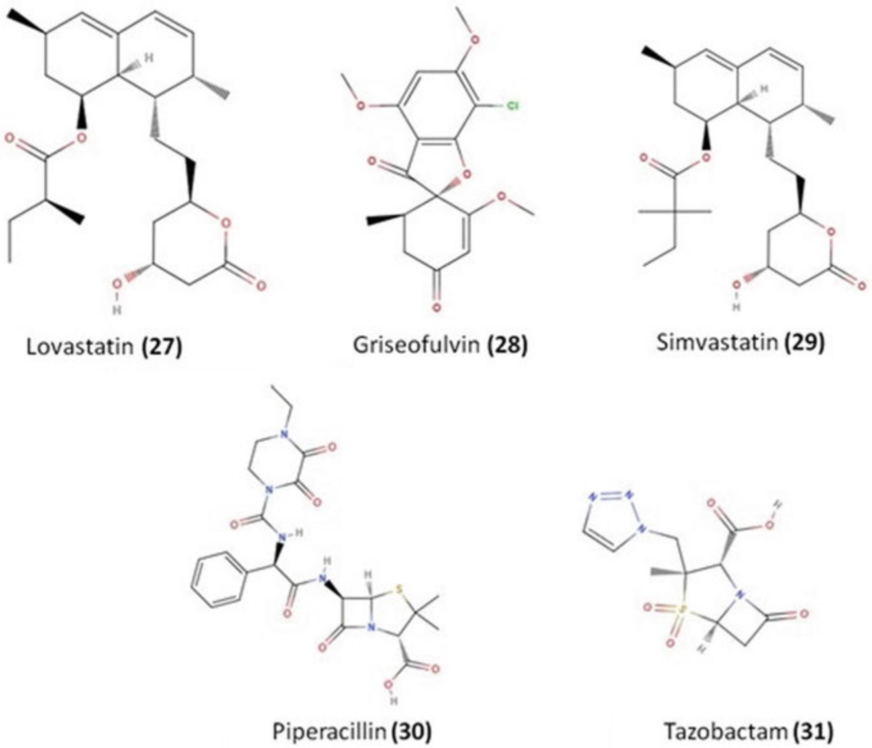


Fig. 14.10 Chemical structures of characteristic fungi-derived drugs that also possess anti-inflammatory properties. Structures were obtained from https://molview.org/ (accessed on April 2, 2023)

mevacor, and its semisynthetic product, simvastatin (**29**) (Fig. 14.10), which is on the market as zocor and simvador. Lovastatin biosynthesis has been reported in several fungal species, including *Aspergillus terreus*, *Monascus purpureus*, *Penicillium citrinum*, *Paecilomyces viridis*, *Penicillium purpurogenum*, *Pleurotus* sp., and *Trichoderma viride*, with the latent being the species used for industrial production.

These statins block 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and prevent the conversion of mevalonate into cholesterol, being the most frequently used drugs in the treatment of hypercholesterolemia to reduce the risk of cardiovascular diseases and to manage abnormal lipid levels by inhibiting the endogenous production of cholesterol in the liver. Another fungi-derived statin is compactin, which is produced by the fungi *P. citrinum* and *Penicillium solitum* and is commercially available as pravachol, selektine, or lipostat, while it also reduces the risk of cardiovascular diseases through the same pathway and is also used as a substrate for the biotransformation or partial chemical synthesis of mevastatin.

Additional studies have indicated several important pleiotropic applications of statins, with lovastatin for example to be used as an antimicrobial and agent for treatments of cancers and bone diseases (Conrado et al. 2022). Nevertheless, apart from their proposed beneficial cardioprotective properties through lowering cholesterol levels, recent studies have also demonstrated several side effects of statin use, such as diabetes mellitus, cancer, early premature cataracts, hearing loss, suicidal ideation, peripheral neuropathy, depression, benign intention tremors and Parkinson's disease, pulmonary interstitial pneumonitis and dysfunctional breathing, interstitial cystitis and bladder wall instability, herpes zoster, impotency, and cognitive impairments, while several researchers have also suggested that statin treatment ultimately offer little protection against cardiovascular risk by their effects on cholesterol levels (Sultan et al. 2019).

Interestingly, some but not all statins, including simvastatin with an intact lactone ring, have also exhibited in vitro a strong anti-inflammatory inhibitory effect against the pro-inflammatory and thrombotic mediator, platelet-activating factor (PAF), and its inflammatory signaling in platelets. Moreover, incubation of human mesangial cells in the form of simvastatin with an intact lactone ring resulted in decreased PAF biosynthesis toward reduced PAF levels. Furthermore, in six simvastatin-treated volunteers a reduction in PAF biosynthesis was observed in their leukocytes explaining the lower levels of PAF in the blood of these subjects, while total cholesterol and low-density lipoprotein cholesterol were also significantly decreased. Within the same period of this administration, high-density lipoprotein cholesterol, triacylglycerol, the effective concentration (EC_{50}) for inducing 50% of PAF-induced plasma-rich platelet aggregation, and lag time of plasma oxidation were unaffected in these participants. Since PAF is implicated in several inflammation-related chronic disorders, the observed anti-inflammatory and cardioprotective anti-PAF effects of statins should be further evaluated as part of their pleiotropic activities, which can provide novel perspectives on the use of statins against chronic disorders (Tsantila et al. 2011).

Griseofulvin is a natural product that was first discovered and isolated from *Penicillium griseofulvum*. In addition to *Penicillium*, griseofulvin may be isolated from other genera of ascomycetes. Griseofulvin has a wide range of applications, from agriculture to medicine. In medicine, griseofulvin has been widely used as an antifungal drug and in treating ringworm and dermatophyte infections in humans and animals due to its low toxicity. This fungistatic has gained increasing interest for multifunctional applications in the last decades due to its anticancer and antiviral potential (Aris et al. 2022). Moreover, it has recently been found that griseofulvin has exhibited indirect anti-inflammatory protection against the inflammatory burden of SARS-CoV-2 infection, through its vasodilation and increased capillary blood flow effects, by beneficially affecting the ACE2 signaling of the renin–angiotensin–aldosterone system (RAAS) toward reduction in inflammation. It seems that griseofulvin binds to ACE2 and competes against SARS-CoV-2 binding to the extracellular domain of ACE2, therefore improving ACE2 vasodilation and tissue protection anti-inflammatory functions. These findings suggest that griseofulvin and its derivatives might be considered when developing future SARS-CoV-2 treatment options (Aris et al. 2022).

Further studies reported the effectiveness of griseofulvin in the treatment of non-fungal skin inflammation diseases, suggesting that it may also have anti-inflammatory and immunomodulatory potential. This is while, earlier studies have shown that griseofulvin is effective in treating shoulder-hand syndrome and a few other inflammatory, rheumatic conditions, such as posttraumatic reflex dystrophies and scapulohumeral periarthritis. Additionally, griseofulvin has been shown effective for inflammatory skin diseases through inducing inhibitory effects on vascular cell adhesion molecule 1 (VCAM-1) in both TNF-alpha and IL-1 stimulated human dermal microvascular endothelial cells (HDMEC) (Aris et al. 2022).

3.6.2 Fungi-Derived Antibiotics with Anti-Inflammatory Properties

Apart from their general and well-established antimicrobial actions, several antibiotics have also exhibited specific anti-inflammatory and antithrombotic potency. For example, the semisynthetic derivatives of penicillins, the firstly reported fungi-derived β-lactam antibiotics originally obtained from *Penicillium* molds, principally *P. chrysogenum* and *P. rubens*, namely the β-lactam antibiotic piperacillin (**30**) and the beta-lactamase antibiotic tazobactam (**31**) (Fig. 14.10), which are widely used in combination for the management and treatment of serious, hospital-acquired infections, including sepsis, were also found to possess strong anti-inflammatory and antithrombotic properties against the activities and the synthesis of the inflammatory and thrombotic mediator, PAF, and in lesser potency against thrombin (Tsoupras et al. 2011a).

More specifically, the combination of piperacillin–tazobactam inhibited strongly PAF-induced aggregation of both washed rabbit platelets and rabbit plasma-rich platelets in a concentration-dependent manner, while when combined with other antibiotics such as netilmycin and amikacin, they synergistically inhibited more potently PAF actions in these cells. Higher concentrations of these antibiotics were needed in order to inhibit platelet aggregation induced by the classic thrombotic mediator, thrombin, suggesting that they have higher specificity against the PAF-related signaling pathway of inflammation and thrombosis. In addition, these antibiotics were also able to inhibit PAF synthesis of rabbit leukocytes, suggesting that they can also reduce PAF levels during inflammatory activation of leukocytes and platelets. These newly found properties of fungi-derived antibiotics used in sepsis suggest that apart from their general actions, these drugs may present additional beneficial anti-inflammatory and antithrombotic effects against the onset and establishment of sepsis and of other microbial-induced inflammatory manifestations and associated disorders, by inhibiting the PAF/PAF receptor inflammatory and thrombotic signaling and/or the thrombin/protease-activated receptor-1 thrombotic signaling, as well as by reducing PAF levels through both PAF biosynthesis inhibition and PAF catabolism induction (Tsoupras et al. 2011a). These promising in vitro results need to be further studied and confirmed by in vivo tests, in order to optimize the efficacy of antibiotic treatment in sepsis and other microbial-induced inflammatory conditions.

3.7 Other Fungi Metabolites with Anti-Inflammatory Properties and Health Benefits

Apart from all these bioactive metabolites, a variety of several other molecules of different structures and activities have also been found in fungi, with a direct or indirect anti-inflammatory and antithrombotic potential (Fig. 14.11). Classic example of such molecules is cinnabarinic acid (**32**). *Pycnoporus*, a white-rot basidiomycete mushroom, secretes enzymes and pigments that break down cellulose, hemicelluloses, and lignin. Specifically, the species *P. sanguineus* produces cinnabarinic acid, which is highly effective at inhibiting the growth of bacteria and common foodborne pathogens. Cinnabarinic acid has been proposed as a potential therapeutic agent in the treatment of neuroinflammatory diseases. Given these powerful properties, *Pycnoporus* should be further studied for applications in food and medicine (Shankar and Sharma 2022; Fazio et al. 2017).

Fungi are classified based on the presence of the essential long-chain polymer, chitin, and its derivative chitosan (**33**). Like other fungal-derived compounds, they possess antimicrobial effects and research has suggested they could be used for the production of new therapeutics with antitumor, anti-inflammatory, and anti-hypertensive activities (Rousta et al. 2023).

Another structural component of many microbial organisms like fungi, yeasts, and mushrooms is β-glucan (**34**). This glucose polymer is a common ingredient in skin care products due to its positive effects on wound healing, skin moisture, and oxidative stress. Additionally, β-glucan has been proposed as a treatment for several health conditions including, cancer, inflammatory bowel disease, and arthritis (Rousta et al. 2023).

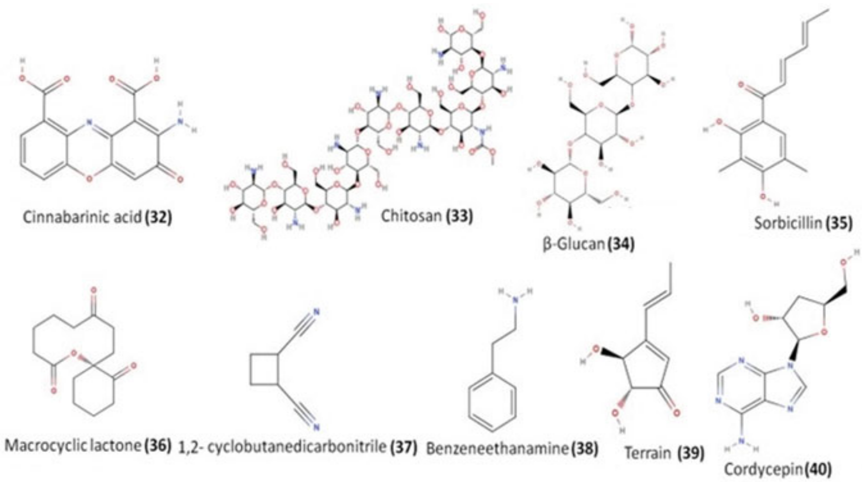


Fig. 14.11 Chemical structures of other fungi metabolites with anti-inflammatory properties. Structures were obtained from https://molview.org/ (accessed on April 2, 2023)

Hexaketide metabolites known as sorbicillinoids were initially discovered in 1948 as a penicillin contaminant. It is composed of the base sorbicillin (**35**) structure with cyclization at the carboxylate terminus. Great advances have been made in the structural elucidation of sorbicillinoids derived from fungi with 62 additional structures discovered between 2016 and 2021. These compounds have many bioactivities, including anti-inflammatory, antiviral, cytotoxic, and antibacterial characteristics. Fungi from the *Pezizomycotina subphylum* of the *Ascomycota phylum*, including species like *Aspergillus* sp., *Penicillium notatum*, and *Trichoderma* sp., generate sorbicillinoids. From maritime habitats, certain sorbicillinoid-producing fungus have been isolated. Due to their health-promoting properties, fungal sorbicillinoids have shown great potential in the pharmaceutical industry (Conrado et al. 2022).

Both macrocyclic lactone and macrocyclic ketone (**36**) were recently isolated from filamentous fungi from various species of *Curvularia*. They have been posed as potential bioactive compounds for application in agricultural and pharmaceutical industries. They seem to possess radical scavenging properties contributing to antioxidant effects. Additionally, they have been found to possess anti-inflammatory and anticancer activities (Mehta et al. 2022).

A. alternata has been found to produce bioactive endophytes, which have potential to inhibit the HIV and reduce the viral load. Specifically, 1,2-cyclobutanedicarbonitrile (**37**) and benzeneethanamine (**38**) have been found to possess anti-inflammatory, antimicrobial, and antioxidant properties. Thus, these bioactive compounds have potential to serve as treatments for HIV infection (Nzimande et al. 2022).

In vitro studies have demonstrated the anti-inflammatory and antioxidant properties of terrain (**39**), a secondary metabolite produced by *A. terreus.* These significant medicinal properties, combined with the high initial yield of this metabolite, facilitate large-scale production and technological advancements in the crude extract of *A. terreus* for the prevention of certain non-transmissible chronic disorders (NTCDs) associated with aging (Takahashi et al. 2020; Asfour et al. 2019; Lee et al. 2015).

Cordyceps militaris is a well-known mushroom that possesses beneficial nutraceutical properties and produces several metabolites. The global market offers numerous nutraceuticals containing cordyceps that support the immune system, vascular system, cognition, anticancer and antioxidant activities, and mental health. The primary metabolite produced by *C. militaris*, cordycepin (**40**), is effective in reducing hyperlipidemia and the accumulation of LDL, total cholesterol, triglycerides, and other lipids caused by high-fat diets. Cordycepin has various pharmacological properties, including anti-inflammatory, immunomodulatory, antioxidant, anti-aging, anticancer, antiviral, cardio, and hepatoprotective effects. *Cordyceps sinensis*, which contains cordycepin, stimulates the production of interleukin-10, an anti-inflammatory cytokine. Cordycepin products, which contain adenosine receptor agonists, are being studied as potential treatments for COVID-19 pneumonia and brain protection (Takahashi et al. 2020; Ashraf et al. 2020).

4 Plant-Derived Compounds from Fungal Endophytes with Potential Anti-Inflammatory and Antithrombotic Benefits

Many plant-derived compounds are actually synthesized by symbiotic/parasitic fungi living inside plants, called endophytes, rather than by the plants themselves. In recent years, increasing researchers have demonstrated the ability of endophytic fungi derived from important medicinal plants to produce the same bioactive metabolites as their host plants. It is now established that endophytes can produce, induce, and modify a variety of plant-derived metabolites inside and outside of host plants, which opens up new possibilities for producing medicinal compounds from endophytes, since only a small fraction of plant species have been studied for their endophytes and their produced bioactives. Thus, as the demand for natural products increases endophytes are becoming more attractive targets for isolating typical host-derived compounds. Given that medicinal plants are a rich source of therapeutic compounds, exploring their endophytes is crucial for identifying and isolating such compounds (Singh et al. 2021; White 2018; Xingyuan et al. 2022). Characteristic examples are nonribosomal peptides, polyketides, terpenes, alkaloids, coumarins, flavonoids, lignans, saponins, quinones, xanthones, and miscellaneous compounds, for which their health benefits and mode(s) of action have been extensively presented elsewhere by Singh et al. (2021), Toghueo (2019), and Nicoletti and Fiorentino (2015). Moreover, many anti-inflammatory compounds currently isolated from medicinal plants have been identified in the metabolome of endophytic fungi. We are presenting in this section a few numbers of well-established and promising bioactive metabolites with anti-inflammatory and antithrombotic potential, which are produced by the interaction(s) of endophytes with their host plants, as summarized in Table 14.1, along with subsequent associated health benefits and/or putative side effects.

5 Conclusions

Within this chapter, it was presented that bioactive fungi metabolites, such as phenolics, bioactive polar lipids, alkaloids, terpenoids, and other miscellaneous compounds, are a new type of promising products for drug and supplements' development with multi-purpose and multi-target aspects, as these active substances do not regulate the inflammatory response through a single reaction path, rather than through their pleiotropic protective effects against several thrombo-inflammatory signaling pathways. The research on the action mechanism of modern pharmacological research shows that bioactive secondary metabolites produced from natural fungi or by engineered species can effectively interact with relevant immune cells, inflammatory factors, and intestinal flora, play an anti-inflammatory role, possess antithrombotic benefits and repair the inflammatory reaction disorder of the body.

Table 14.1 Bioactive metabolites derived from the interaction(s) between plants and fungal endophytes, with anti-inflammatory and antithrombotic potential and several other health benefits

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
Piperine	• Inhibition of LPS—induced expression of IRFs and its associated pro-inflammatory responses, such as inhibition of PGE2 and NO.	• Anticancer.	• In high doses it might slow blood clotting and thus might increase the risk of bleeding in people with bleeding disorders.	*Piper longum, Piper nigrum*	*Periconia sp.*	*Piper longum*	Singh et al. (2021), Verma et al. (2011), Chithra et al. (2014a, b), Chithra et al. (2017), Stojanović-Radić et al. (2019), Park et al. (2007), Ziegenhagen et al. (2021)
	• Inhibition of platelet aggregation induced by collagen, AA, and PAF.	• Antimicrobial.	• Bioavailability-enhancing ability for certain drugs that can increase the risk of unintended deleteriously increased or adverse drug effects.		*Colletotrichum gloeosporioides*	*Piper nigrum*	
	• Decrease of TNF-α, inducible iNOS, and COX-2.	• Antidepressant.	• In high doses it can cause disturbance of spermatogenesis and of maternal reproductive and embryotoxic effects.		*Mycosphaerella* sp.	*Piper nigrum*	
	• Inhibition of IL-1β, TNF-α, IL-6, expression of iNOS, activities of MMP-3 and MMP-13, of mRNA expression for ADAMTS-4, and ADAMTS-5.	• Hepatoprotective.			*Phomopsis* sp.	*Oryza sativa*	
	• Reduction in activation of the STAT1 and its associated inflammatory signal transduction pathways involved in	• Bioavailability-enhancing ability for certain drugs and nutrients.					

	different pathologies correlated to the inflammatory process.						
	• Inhibition of the release of Th-2-mediated cytokines involved in inflammatory cascades.						
Aconite-like alkaloids (i.e., aconitine)	• Inhibition of inflammatory pathways induced by histamine, serotonin, acetic acid, carrageenan.	• Anticancer.	• Cardiotoxic.	*Aconitum* spp.	*Cladosporium cladosporioides*	*Aconitum leucostomum*	Singh et al. (2021), Yang et al. (2013), Singhuber et al. (2009), Hikino et al. (1980), Hikino et al. (1982), and Zhao et al. (2012)
• Subsequent inhibition of inflammation-induced increased vascular permeability and/or edema formation.		• Analgesic.	• Bradycardia.				
• Can protect the heart, platelets, and vascular smooth muscle in DIC.		• Anti-neuralgic.	• Hypotension.				
			• Ventricular dysrhythmia.				
			• Neurotoxic.				
			• Inhibition of release of neurotransmitters.				
Sanguinarine	• Inhibition of monocyte attachment to cytokine-activated HUVEC by inhibiting PAF synthesis induced by TNF-α and IL-1β.	• Anticancer.	• Toxicant.	*Macleaya cordata, Sanguinaria canadensis*	*Fusarium proliferatum*	*Macleaya cordata*	Wang et al. (2014), Singh and Sharma (2018), Park et al. (2014), Shu et al. (2021), Jeng et al. (2007), Lou et al. (2021), and Sneddon et al. (2006)
	• Inhibition of tumor invasiveness-induced inflammatory manifestations by inhibiting the expression of MMP-9 and COX-2.	• Antimicrobial.	• Hepatotoxic.				

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	• Inhibitory effect on the collagen pathway of platelet activation and aggregation, and reduction in thrombus formation.	• Antioxidant.	• Pro-apoptotic properties in normal cells (through several mechanisms, including its action on the Na + -K + -ATPase transmembrane protein).				
	– Inhibition of the phosphorylation of multiple components in the collagen-specific receptor GPVI signaling pathway.	• Anthelmintic.	• Induce apoptosis and adversely influence embryonic development.				
	– Inhibition of collagen-induced increase in the intracellular Ca2+ concentration ([Ca2+]i).	• Neuroprotective.	• Carcinogen (might be associated with pre-carcinoma within oral or skin potentially).				
	– Inhibition of integrin αIIbβ3 outside-in signaling via reducing β3 and Src (Tyr-416) phosphorylation.	• Cardioprotective, when an excess of activated platelets is involved.					
	– Inhibition of platelet activation and aggregation induced by arachidonic acid, collagen, U4619,						

Plant-derived phenolics—coumarins	*Anti-inflammatory and antithrombotic bioactivities, molecular targets, and mode(s) of action*	*Other health benefits*	*Putative side effects—toxicity*	*Plant source*	*Endophytic source*	*Host plant*	*Reference*
	and thrombin, by activating adenylate cyclase, by inhibiting platelet Ca^{2+} mobilization, TXB2 production, as well as by suppressing COX-1 enzyme activity.						
Capsaicin	• Inhibition of adipose tissue inflammatory responses via decreasing adipose tissue macrophages and levels of inflammatory adipocytokines (TNF-α, MCP-1, IL-6, and leptin].	• Antilithogenic.	• Potent irritant—can cause irritation, pain, and burning of mucous membranes.	*Capsicum annuum* (red pepper)	*Alternaria alternata*	*C. annuum*	Devari et al. (2014), Choi et al. (2000), Hogaboam and Wallace (1991), Munjuluri et al. (2021), and Chang et al. (2023)
	• Inhibition of PAF-induced superoxide production by inhibiting PAF-activated elicited SOCE via PLC activation, which results in inhibiting the subsequent superoxide production.	• Thermogenic.	• Topical patch administration can cause local erythema, pain, edema, and other relevant adverse effects.				
	• Inhibition of platelet activation and aggregation induced by PAF, thrombin, and calcium ionophore (A23187).	• Gastro-stimulatory. • Antidiabetic. • Cardioprotective. • Anticancer.	• Vasoconstrictive effects in people with underlying inflammatory conditions.				

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
Isofraxidin	• Depletes infiltrating inflammatory cells (Kupffer cells and macrophages) and inflammatory cytokines (TNF-α and IL-6) in liver cells.	• Antioxidant.	Minimal cytotoxic side effects	*Acanthopanax senticosus or Eleutherococcus senticosus,*	*Biscogniauxia cylindrospora*		Yamazaki and Tokiwa (2010), Yim et al. (2017), Majnooni et al. (2020), Lin et al. (2020), and Chen et al. (2020)
	• Reduces inflammation mediators (COX-2, NO, PGE2, and iNOS) and cytokines (TNF-α and IL-6), as well as the expression of MMP-3 and MMP-13 and NF-κB activation in human cells that were induced with IL-1β.	• Anticancer and cytotoxic activities.		*Apium graveolens* (Siberian ginseng)			
	• Downregulation of several signaling pathways including NO, PGE2, TNF-α, IL-6, ADAMTS, COX-2, iNOS, MMPs, NF-kβ, and TLR4 for the treatment of inflammatory diseases such as osteoarthritis and pain.	• Cardioprotective effects.					

	• Inhibits NLRP3 inflammasome and thus exhibits cardioprotective effects and alleviates MI.	• Anti-hypertension effects.					
	• Inhibits platelet aggregation and activation induced by ADP, AA, and collagen.	• Hypolipidemic (regulates lipid metabolism, by reducing triglyceride accumulation and release of associated signaling molecules and thus protects from related disorders, and reduces hepatic lipogenesis).					
	• Ameliorates influenza virus A-induced lung inflammation, as well as it reduces the expressions of platelet activation biomarkers (P-selectin and CD61), decreases the serum levels of TNF-α, IL-1β, IL-6, and MIP-2, suppresses peripheral platelet aggregation, and prolongs the survival time of infected animals.	• Potent hyperpigmentation agent.					
Umbelliferone	• Reduction in inflammation-induced elevated levels of hepatic and cerebral NO,	• Antioxidant.	Minimal cytotoxic side effects	*Artemisia scoparia,*	*Penicillium* sp.	*Avicennia*	Yu et al. (2015), Germoush et al. (2018), Wang et al. (2019), Wang et al.

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	TNF-α, IL-1β, and glutamine.						(2015), Muthu et al. (2016), Chen et al. (1995), Cruz et al. (2020), Mazimba (2017), and Sim et al. (2015)
	• Suppresses hepatic LPS binding protein, TLR4, NF-kB, and TNF-α levels and gene expression increases in response to chronic alcohol intake.	• Anti-hyperglycemic.		*Scopolia carniolica*			
	• Reduces tumor-induced inflammatory markers (TNF-α and IL-1β) in colon carcinogenesis.	• Antimicrobial.		*(syn. Scopolia japonica),*			
	• Alleviates LPS-induced inflammatory responses by downregulating TLR4/MyD88/NF-κB signaling.	• Anticancer.		*Viburnum prunifolium*			
	• Ameliorates cerebral ischemia–reperfusion injury via upregulating the PPAR-γ expression and suppressing NLRP3 inflammasome.	• Hepatoprotective.					
	• Inhibition of LOX and COX.	• Antidiarrheal and antiulcerogenic.					

	• Inhibits platelet activation and aggregation induced by AA, collagen, and PAF.	• Protector against the side effects of anti-inflammatory agents.					
Plant-derived Phenolics—flavonoids	*Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action*	*Other health benefits*	*Putative side effects—toxicity*	*Plant source*	Endophytic source	*Host plant*	*Reference*
Quercetin	• Inhibits PAF activities and PAF synthesis, while it induces PAF catabolism, and subsequently ameliorates PAF-related inflammatory signaling and associated inflammatory manifestations.	• Antioxidant.	• Rarely reported.	*Fruits, vegetable*	*Aspergillus nidulans, Aspergillus oryzae*	*Ginkgo biloba*	Cheng et al. (2012), Qiu et al. (2010), Ebada et al. (2016), Srivastava et al. (2016), Colunga Biancatelli et al. (2020), Marunaka et al. (2017), Costa et al. (2016), Gormaz et al. (2015), Morikawa et al. (2003), Pace-Asciak et al. (1995), Balestrieri et al. (2003), and Vallance et al. (2019)
	• Inhibitory effects on AA and on the activity and production of the leukotriene/prostaglandin pathways' associated pro-inflammatory mediators, such as LOX, COX, TNF-α, and PLA2.	• Anticancer.	• May cause mild headache and upset stomach.		*Annulohypoxylon squamulosum*	*Cinnamomum*	
	• Suppression of PGE2, TNF-α, RANTES, MIP-2, and the mRNA for COX2 in carrageenan induced inflammation.	• Antiviral.	• Some interactions with certain drugs leading to altered drug bioavailability that might interfere with the effects of medication.		*Nigrospora oryzae*	*Loranthus micranthus* sp.	
	• Reduces the production of IL-1α, IL-6, IL-8, TNF-α, and PARP-1, and downregulating VCAM-1.	• Antidiabetic.					

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	• Reduces LPS-induced release of NO and inflammatory cytokines via induction of PON2 which also possesses anti-inflammatory activity.	• Cardioprotective.					
	• Decrease in thrombin formation in platelets.	• Neuroprotective.					
	• Inhibition of platelet aggregation induced by thrombin, ADP, TXA2, collagen, PAF, AA, and U46619 (a synthetic TxA2 mimetic).	• Antiallergic.					
	• Inhibitor of multiple kinases involved in platelet activatory signaling pathways.	• Anti-hypertensive (via anti-inflammatory and anti-oxidant actions, as well as via regulation of ion transporters and channels).					
	• Inhibits calcium mobilization induced by a low dose of thrombin, ADP, collagen, and U46619, and subsequently it reduces PS enrichment of platelets' surface, and the						

	associated thrombin generation.						
	• Antagonistically blocks TxA2 receptors and thus TxA2 signaling for platelet activation.						
	• Inhibits TxB2 production in platelets in response to collagen, and it reversibly inhibits COX-1 and the conversion of AA to prostaglandin H2 (PGH2) by preventing its entry into the active site of COX-1, while it also inhibits thromboxane synthase required to convert PGH2 into TxA2.						
Curcumin	• Influences/modulates inflammatory chemokines and chemokine receptors toward anti-inflammatory protection of several inflammation-related disorders.	• Anti-inflammatory protection and preventive properties in healthy subjects, aged subjects, and menopausal women.	• In general, safe, well-tolerated, and without any adverse side effects.	*Curcuma* spp.	*Chaetomium globosum*	*Curcuma wenyujin*	Rakha et al. (2022), Wang et al. (2012b), Yan et al. (2014), Fadus et al. (2017), Shah et al. (1999), Hussain et al. (2022), and Panknin et al. (2023)
	• Prevent atherosclerosis and platelet aggregation.	• Antioxidant.	• The intended use of curcumin as a food additive is generally recognized as safe by the U.S. Food and Drug Administration.				

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	• Through regulating many processes involved in platelet aggregation, curcuminoids collectively demonstrated detectable antiplatelet activity.	• Antitumor and anti-angiogenetic.	• As a component of turmeric, curcumin may interact with prescription drugs and dietary supplements.				
	• Lowers platelet and leukocyte adhesion.	• Anti-atherosclerotic and cardioprotective.	• In high amounts, it may be unsafe for women during pregnancy.				
	• Modulates the endothelium to reduce platelet adhesion.	• Neuroprotective.	• It may cause side effects, such as nausea, diarrhea, hives, or dizziness.				
	• Inhibits the expression of platelet/endothelial cell adhesion molecule 1, netrin G1, delta-like 1, and plasma cell endoplasmic reticulum protein 1, which causes cell adhesion and migration.	• Anti-arthritic.	• Between 2004 and 2022, there were 10 cases of liver injury caused by cucumin herbal and dietary supplement.				
	• Inhibit activation of platelets to form thrombosis/embolism, reduces P-selectin, E-selectin, and GP	• Anti-inflammatory protection against chronic liver diseases.	• Curcumin is a contact allergen.				

	IIb/IIIa and inhibits PDGF.						
	• Inhibits platelet aggregation induced by PAF, AA, collagen epinephrine, and ADP.	• Antidiabetic.	• Preliminary clinical studies in cancer patients consuming high doses of curcumin (up to 8 grams per day for 3–4 months) showed no toxicity, though some subjects reported mild nausea or diarrhea.				
	• Suppresses TXB2 production and inhibits TXA2 and mobilization of intracellular Ca2+ and associated signaling in platelets, and elevates prostacyclin and 12-LOX enzyme activities.	• Protects against gastrointestinal disorders.					
	• Reduces acute inflammation brought on by carrageenan.	• Protects against inflammatory manifestations of persistent infections (periodontitis, gingivitis, stomatitis, COVID-19, HIV infections, etc.)					
	• Downregulates of COX-2, LOX, TNF-α, IL-1, IL-2, IL-6, IL-8, and Janus kinases.	• Protects against inflammatory manifestations of autoimmune disorders (rheumatoid arthritis, multiple sclerosis, psoriasis, etc.)					
	• Downregulates the expression of pro-inflammatory cytokines and chemokines via NF-kB inactivation.	• Anti-lipidemic and anti-hypercholesterolemic.					
	• Reduced mortality and coagulopathy	• Beneficial effects on clinical outcomes					

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	induced by infections and LPS-induced intravascular coagulation by decreasing TNF-α level.	and/or biomarkers of obesity-associated metabolic disorders or musculoskeletal disorders, where inflammation is a key driver.					
Kaempferol	• It blocks the expression of inflammatory cytokines (IL-1B and TNF-α), COX-2 protein, and inducible NO synthase (iNOS).	• Antitumor.	• Rarely reported.	*Fruits, vegetables, medicinal herbs*	*Annulohypoxylon boveri var. microspora*	*Cinnamomum* sp.	Vallance et al. (2019), Sadeghi et al. (2023), Hegde et al. (2023), Chaturvedi et al. (2014), Huang et al. (2014), Chen and Chen (2013), and Imran et al. (2019)
	• Suppress the inflammatory responses, in LPS-stimulated inflammation via NF-κB and MAPK pathway, and inhibition of inflammatory factors such as iNOS, COX-2, TNF-α, and IL-6.	• Chemopreventive agent in cancer treatment.	• Poor oral bioavailability, which is increased by the use of nanocarriers.		*Annulohypoxylon squamulosum*	*Tylophora indica*	
	• Reduces the Th2 inflammatory cytokines.	• Antibacterial.	• High intake may cause adverse side effects. For example, in tumor patients who are deficient in iron and/or folic acid may exhibit abnormal side effects, since it reduces the		*Fusarium chlamydosporum*	*Podophyllum hexandrum*	
	• Inhibitory effects against platelet activation stimulated by thrombin, collagen, AA, ADP, and PAF.	• Antidiabetic.			*Mucor fragilis*		
		• Antioxidant.					

	• Inhibits pro-coagulant protein-ase activity, fibrin clot formation, blood clot and thrombin (or collagen/epineph-rine)-stimulated platelet activation, thrombosis, and coagulation.	• Cardioprotective. • Neuroprotective. • Hepatoprotective. • Antiallergic.	bioavailability of iron and/or reduces the level of folic acid in the cells.				
Rutin	• Inhibition of expression of COX-2 and iNOS via inhibition of p38 MAPK and c-Jun N-terminal kinase (JNK), and decreases the secretion of TNF-α.	• Antioxidant.	• Generally consid-ered safe when con-sumed in the amounts found in foods.	*Aegle marmelos*	*Anonymous*	*Pteris multifida, Nerium olean-der, Ginkgo biloba, Aegle marmelos*	Balestrieri et al. (2003), Choi et al. (2015a), Ren et al. (2019), Fan et al. (2007), Ganeshpurkar and Saluja (2017), Enogieru et al. (2018), Rakotondrabe et al. (2023), Zaragozá et al. (2021), Sheu et al. (2004), Choi et al. (2021), and Choi et al. (2015b)
	• Upregulates SIRT-1, Nrf-2, and HO-1 and downregulates JAK-2/STAT3 pathways, as well as inflammatory markers.	• Anticancer.	• Higher doses of rutin in supplements may cause specific side effects, including headache, rashes, muscle tension changes in heartbeat, a high white blood cell count (leukocytosis), blurred vision, fluid accumulation in knees, upset stomach.	*Ginkgo biloba,*	*Chaetomium* sp.		
	• Reduces the levels of pro-inflammatory bio-markers and cytokines (NO, PGE2, TNF-α, and IL-6).	• Neuroprotective.	• May interact with medications for diabetes; people with diabetes should monitor blood sugar levels closely, especially if adding rutin to a	*Nerium oleander,*	*Xylaria* sp.		

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
			regimen that already includes blood sugar-lowering medications.				
	• Inhibits dense granule secretion in platelets.	• Mitigates hyperglycemia and hyperlipidemia, while increasing insulin amount.	• Should be avoided if you have been prescribed warfarin, as it may reduce the medication's anticoagulant (blood thinning) effect.	*Pteris multifida*	*Aspergillus flavus*		
	• Antiplatelet activity through the blocking of fibrinogen GPIIb/IIIa receptors, the suppression of the platelet activation, as well as the pro-aggregate effect of calcium ionophore.	• Reduces the induced damage of the kidney, liver, and pancreas.					
	• Inhibition of platelet aggregation induced by ADP, collagen, and PAF.	• Cardioprotective.					
	• Antiplatelet activity through inhibition of activation of phospholipase C, followed by inhibition of protein kinase C activity and TXA2 formation, thereby leading to inhibition of the phosphorylation of P47	• Protects against metabolic disease.					

	and intracellular Ca(2+) mobilization, finally resulting in inhibition of platelet aggregation in platelets stimulated by collagen or PAF.						
	• Reduces fibrin clot and prolongs aPTT, PT, and CT, and decreases the activity of pro-coagulant protein, thrombin.	• Anti-arthritic.					
	• Protective effect against collagen and epinephrine (or thrombin) induced acute thromboembolism.						
Silymarin	• Anti-inflammatory actions via ameliorating the release and levels of inflammatory and immunological biomarkers and cytokines, such as CRP, TNFα, INF-γ, IL-6, IL-1β, and IL-12β, as well as by impairing NF-κB-dependent transcription and by impeding NLRP3 inflammasome activation.	• Anticancer—antimetastatic.	• Can lead to disruptions of the thyroid system by blocking the uptake of thyroid hormones into the cells by their receptors. Subsequently, the administration of silymarin during pregnancy is especially thought to be dangerous, potentially leading to the Allan–Herndon–Dudley syndrome, a brain development disorder that causes both moderate-to-severe intellectual disability and problems with speech and movement.	*Silybum marianum*	*Aspergillus iizukae*	*Silybum marianum*	Chen et al. (2002), Ganeshpurkar and Saluja (2017), Ramasamy and Agarwal (2008), Vargas-Mendoza et al. (2014), Dixit et al. (2007), Karimi et al. (2011), El-Elimat et al. (2014), Breschi et al. (2002), Stanca et al. (2013), De La Lastra et al. (1992), Rui (1991), Pourová et al. (2019), and Zhang et al. (2023)
		• Antioxidant.					

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	• Anti-inflammatory properties in cirrhotic liver by reducing the expression and levels of PAF-biosynthetic enzymes.		• Asymptomatic liver toxicity (hyperbilirubinemia and elevation of alanine aminotransferase) in prostate cancer patients.				
	• Inhibits platelet aggregation induced by collagen, AA, and ADP, the transformation of prostaglandin H2 to TXA2 by thromboxane synthase and antagonistically inhibits thromboxane receptors, while it also decreases the expression of platelet activation markers, such as P-selectin and an active form of αIIbβ3.	• Cardioprotective.	• Is also devoid of embryotoxic potential.				
	• Influence human blood coagulation by decreasing the platelet aggregation via inhibition of the COX activity.	• Hepatoprotective—antihepatitic.					
	• Membrane-stabilizing action preventing or inhibiting membrane peroxidation of fatty	• Antiallergic.					

	acids and subsequent inflammation by inhibiting LOX and the formation of associated prostaglandins.						
	• Anti-inflammatory and antioxidant properties against ALD, NAFLD, and hepatocellular carcinoma, by regulating the activation of including AMPK, Farnesoid X receptor, nuclear factor erythroid 2-related factor-2, PPARs, phosphatidylinositol-3-kinase, and lysyl oxidase-like proteins, and their associated signaling pathways.	• Neuroprotective.					
	• Anti-ulcerogenic effect of silymarin related to its inhibitory mechanism of enzymatic peroxidation by the LOX pathway, avoiding leukotriene synthesis.	• Antidiabetic. • Antiviral. • Anti-hypertensive. • Immunomodulatory. • Photoprotective. • Detoxification.					
Apigenin	• Inhibits PGE2, COX-2, IL-1β, and IL-6 and downregulates the COX-2 expression and activity via	• Antioxidant.	• In general, it is safe and tolerable in a variety of in vivo and in vitro studies and clinical trials.	*Matricaria* spp. *and vegetables*	*Chaetomium globosum*	*Cajanus cajan*	Balestrieri et al. (2003), Wadhwa et al. (2022), Johannes et al. (2016), Shukla and Gupta (2010), Panda and Kar (2007), Gao

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Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	suppressing the LPS-induced protein tyrosine kinase signal transduction.						et al. (2012), Sato et al. (1994), Viola et al. (1995), and Salehi et al. (2019)
	• Inhibits PAF activities and PAF synthesis and subsequently ameliorates PAF-related inflammatory signaling and associated inflammatory manifestations.	• Anticancer.	• It can cause hepatorenal toxic only at high doses of 500 mg/kg and 1000 mg/kg.				
	• Inhibit the release of IL-1β, IL-6, and TNF-α through suppressing the NF-κB signaling pathway.	• Neuroprotective.					
	• Prevents the IκB degradation and nuclear translocation of the NF-κB.	• Regulates hyperglycemia, thyroid dysfunction, and lipid peroxidation.					
	• Activates different anti-inflammatory pathways, including p38/MAPK and phosphatidylinositol 3-kinase (PI3K)/AKT.	• Exerts anxiolytic and sedative effects.					
	• Can inhibit neuroinflammation by suppressing CD38 overexpression.						

	• Inhibits platelet aggregation induced by AA and U46619 (a synthetic TxA2 mimetic).						
	• Inhibits calcium mobilization induced by a low dose of thrombin, ADP, collagen, and U46619, and subsequently, it reduces PS enrichment of platelets' surface and the associated thrombin generation.						
	• Antagonistically blocks TxA2 receptors and thus TxA2 signaling for platelet activation.						
	• Inhibits TxB2 production in platelets in response to collagen, and it reversibly inhibits COX-1 and the conversion of AA to prostaglandin H2 (PGH2) by preventing its entry into the active site of COX-1, while it also inhibits thromboxane synthase required to convert PGH2 into TxA2.						

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	• Inhibitor of multiple kinases involved in platelet activatory signaling pathways.						
Dimer of epicatechin (DoE)	• Anti-inflammatory effects on the inflammatory response of inflammation-induced paw edema by inhibiting carrageenan-induced inflammation.	• Antioxidant.	• In an animal study the effective dosage for survival was found 1.25 g/kg (Gp V) and the lethal dosage was 1.5 g/kg (Gp IV). Above 1.5 g/kg of the DoE produced hypersensitivity, righting reflex, tremors, and convulsions leading to the death of the animal.		*Curvularia australiensis FC2AP*	*Leaves of Aegle marmelos*	Mehta et al. (2022), Attiq et al. (2021), Guo et al. (2023), Mani et al. (2021), and Matsui (2015)
	• Minimizes the accumulation of leukocytes, proteins, and fluids and decreases vascular permeability and cellular infiltration.	• Anticancer.					
	• Inhibits STAT3 activation induced by PDGF.	• Cardioprotective.					
	• Inhibits platelet aggregation.	• Anti-hypertensive.					
		• Anti-obesity.					
		• Antidiabetic.					
Chrysin	• Inhibits PGE2 production in whole blood, due to direct	• Antibacterial.		*Passiflora incarnata*	*Alternaria alternata, Colletotrichum capsici,*	*Passiflora incarnata*	Singh et al. (2021), Cooper et al. (2004), and Santos-Buelga and Scalbert (2000)

	inhibition of COX-2 enzymatic activity.				*Colletotrichum taiwanense*		
	• Inhibits TXB2 production in whole blood, suggesting that it strongly inhibits COX-1 activity.	• Antidiabetic.					
	• Inhibits PAF receptor binding, and thus PAF-associated inflammatory signaling.	• Anxiolytic. • Hepatoprotective. • Anti-aging. • Anticancer.					
Luteolin	• Inhibits PAF activities and PAF synthesis and subsequently ameliorates PAF-related inflammatory signaling and associated inflammatory manifestations and disorders.	• Antioxidant.	• Safe and tolerable in a variety of in vivo and in vitro studies and clinical trials.	*Fruits, vegetables*	*Annulohypoxylon boveri var.*	*Cinnamomum* sp.	Cheng et al. (2012), Pace-Asciak et al. (1995), Shukla and Gupta (2010), Viola et al. (1995), Seetharaman et al. (2017), Saadawi et al. (2012), Jang et al. (2017), Lopez-Lazaro (2009), Zhao et al. (2014), and Lee et al. (2023)
	• Prevents inflammation and allergic response in the lungs and nose by inhibiting inflammatory cytokines: IL-4, IL-5, and IL-13.	• Neuroprotective.	• May have adverse effects for autistic children, people with colitis, and pregnant people	*Medicinal herbs*	*Microspora*	*Cajanus cajan*	
	• Inhibits PGE2, COX-2, IL-1β, and IL-6 and downregulates the COX-2 expression and activity via suppressing the LPS-induced protein tyrosine kinase signal transduction.	• Antimicrobial.			*Aspergillus fumigatus*		

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	• Inhibit the release of IL-1β, IL-6, and TNF-α through suppressing the NF-κB signaling pathway.	• Cardioprotective.					
	• Inhibitory effect on collagen, ADP, thrombin, and U46619-induced platelet aggregation, as well as the adhesion of thrombin-activated platelets to collagen or fibrinogen.	• Antidiabetic.					
	• Suppresses platelet aggregation by inhibiting the TxA2 receptor, and strongly inhibits TxA2 production in agonist-induced platelets.	• Immunomodulatory.					
	• Targets both EGFR and KDR genes that induce the phosphorylation of AKT and the AKT-mediated activation of PI3K, which has been implicated in playing an important role	• Anticancer. • Antiallergic. • Skin protection. • Due to its anti-inflammatory properties, luteolin is being researched as a potential complementary					

	in platelet activation, suggesting that its effect on the PI3K-Akt signaling pathway is highly relevant to its antithrombotic therapeutic effect.	treatment for multiple sclerosis.					
Plant-derived Saponins—Terpenes	*Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action*	*Other health benefits*	*Putative side effects—toxicity*	*Plant source*	*Endophytic source*	*Host plant*	*Reference*
Diosgenin (phytosteroid sapogenin)	• Reduction in the levels of several inflammatory mediators, including NO and IL-1 and IL-6 in LPS/IFN-γ-induced inflammation.	• Antitumor and antiproliferative activities.	• Safe and tolerable in several studies.	*Dioscorea* spp.	*Paecilomyces* sp. *Cephalosporium* sp.	*Paris polyphylla var. Yunnanensis*	Singh et al. (2021), Lu et al. (2021), Yanoshita et al. (1996), Cao et al. (2007), Jesus et al. (2016), Patel et al. (2012), and Gong et al. (2011)
	• Inhibited the extracellular and intracellular superoxide anion generation by blocking the cAMP, PKA, cPLA 2, PAK, MAPK, and AKT signaling pathways.	• Anti-atherosclerotic and cardiovascular protection.	• In high amounts has exhibited toxic effects in animal models as an emerging contaminant, induced transgenerational reproductive toxic effects due to its endocrine disrupting nature.		*Fusarium* sp.	*Dioscorea nipponica*	
	• Reduces the adhesive capacity of vascular smooth muscle cells and the TNF-α mediated induction of ICAM-1 and VCAM-1 in these cells by inhibiting the MAPK/Akt/NF-κB	• Neuroprotective.					

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	signaling pathway and ROS production.						
	• Regulates adipokine expression and ameliorates endothelial dysfunction via regulation of AMPK and thus protects endothelial functions against inflammatory insults.	• Antiallergic.					
	• Inhibits IL-1-β-induced expression of inflammatory mediators, including MMP 3 and 13, iNOS, and COX-2 against skin inflammation, while it also increases the expression of VEGF, angiopoietin, and endothelial tyrosine kinase receptor against rheumatoid arthritis.	• Hypoglycemic.					
	• Antithrombotic activity through improving the anticoagulation function, inhibiting ADP-induced platelet	• Protective effects against metabolic diseases (diabetes, obesity, and dyslipidemia, including					

	aggregation and thrombosis.	hypercholesterolemia) and several infections.					
Ginsenosides (steroid glycosides and triterpene saponins)	• Anti-inflammatory agents by targeting different steps of the NF-κB signaling - pathway, ameliorating the symptoms of severe inflammation-related manifestations and associated illnesses.	• Antioxidation.	• Likely safe when taken for up to 6 months.	*Panax*	*Camarosporium* sp., *Dictyochaeta* sp.	*Aralia elata* *Panax ginseng*	Nicoletti and Fiorentino (2015), Salehi et al. (2019), Zhang et al. (2013), Maurya et al. (2022), Wu et al. (2012), Wu et al. (2013), Luo et al. (2013), Jin et al. (2017), Jang et al. (2023), Huo et al. (2023), and Luo et al. (2020)
	• Participate in anti-inflammatory response by inhibiting the action of inflammatory mediators (iNOS and COX-2) and by downregulating the expression and secretion of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α.	• Antitumor and anti-proliferative effects.	• Hormone-like effects that could be harmful when used long-term (trouble sleeping, severe rash, liver damage, and severe allergic reactions).		*Penicillium* sp.	*Panax notoginseng*	
	• Can inhibit inflammatory factors related to liver fibrosis, including TNF-α, IL-1β, caspase-1, and IL-6, in a JNK- and p38/ERK-dependent manner.	• Cardioprotective.	• Caution is needed in patients with auto-immune disorders that need immunosuppres-sion, since ginsenosides can enhance and increase the activity of the immune system.		*Aspergillus* sp., *Fusarium* sp., *Verticillium* sp. *Aspergillus* sp., *Fusarium* sp.		
	• Anti-inflammatory regulation and activities of immune cells (T cells and macrophages).	• Neuroprotective.	• Caution is also needed in the case of bleeding conditions due to their strong antithrombotic effects.				

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Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	• Influence the NAMPT/NAD+/SIRT, AMPK/SIRT1/PGC-1α, Nrf2/HO-1, PKCs/PARPs/NF-κB, and AMPK/Nrf2/mTOR signaling pathways, thereby regulating NAD+ metabolism to prevent and treat various diseases.	• Antimicrobial.	• Likely unsafe in infants and children (fatal poisoning in newborns).				
	• Antiplatelet effects due to their interference on multiple signal pathways of platelet aggregation induced by thrombin, collagen, ADP, U46619, and PAF, which lead to attenuation on several significant events, including TXA2 production, [Ca2+]i generation, αIIb/β3 activation, ATP release, and MAPK phosphorylation.		• Unsafe when taken by mouth during pregnancy.				
	• Suppression on proliferation and migration of VSMCs, which also help to delay thrombosis.						

Ginkgolides and bilobalide (terpenes)	• Inhibit PAF activities and PAF synthesis and subsequently ameliorates PAF-related inflammatory signaling and associated inflammatory manifestations and disorders.	• Neuroprotective.	• Side effects occur very rarely if preparations from controlled cultivation and standardized processing are used.	*Ginkgo biloba*	*Pestalotiopsis uvicola*	*Ginkgo biloba*	Tsoupras et al. (2020b), Tsoupras et al. (2011b), Luo et al. (2020), Irfan et al. (2020), Valli and Giardina (2002), and Sarkar et al. (2020)
	• Inhibition of STAT-3 pathway in high-glucose-stimulated endothelium.	• Antiallergic.	• Gastrointestinal complaints (bloating, cramps, and heartburn) headache, dizziness, and a general feeling of discomfort.		*Fusarium oxysporum*		
	• Suppression of COX-2, NO, TNF-α, IL-6, and IL-1β during LPS-induced inflammation.	• Analgesic.	• Increased bleeding tendency, platelet dysfunction.				
	• Inhibition of NF-κB activity by NF-κB-specific suppressor IκBα in CCL4-induced inflammatory hepatotoxicity.	• Anti-viral.	• CNS hemorrhage in patient previously stable of warfarin.				
	• Inhibition of IL-6, IL-8, MCP-1, and TNF-α. activation of NF-κB signaling during LPS-induced inflammation.	• Antitumor.	• In pregnancy, they are contraindicated for safe use due to insufficient data.				
	• Antithrombotic-antiplatelet effects against the PAF,	• Anti-atherosclerotic and cardioprotective.					

(continued)

Table 14.1 (continued)

Plant-derived alkaloids	Anti-inflammatory and antithrombotic bioactivities; molecular targets and mode(s) of action	Other health benefits	Putative side effects—toxicity	Plant source	Endophytic source	Host plant	Reference
	thrombin, collagen and ADP-associated pathways of platelet activation-aggregation.	• Protective effects in cardio-cerebral ischemia–reperfusion injuries.					
		• Beneficial against cerebrovascular disease by improving blood flow, reducing ischemia–reperfusion injury or inhibiting platelets.					
		• Hepatoprotective.					

LPS: lipopolysaccharide, *IRFs:* interferon regulatory transcription factors, *PGE1*: prostaglandine-E1, *PGE2*: prostaglandine-E2, *NO*: nitric oxide, *AA*: arachidonic acid, *PAF*: platelet-activating factor, *TNF-α*: tumor necrosis factor alpha, *iNOS*: nitric oxide synthase, *COX-2*: cyclooxigenase-2, *IL-1β:* interleukin 1-beta, *IL-6*: interleukin 6, *MMP*: matrix metalloproteinase, *ADAMTS:* a disintegrin and metalloproteinase with thrombospondin motifs, *STAT1*: signal transducer and activator of transcription 1, *DIC*: disseminated intravascular coagulation, *HUVEC*: human umbilical vein endothelial cells, *MCP-1*: monocyte chemoattractant protein-1, *SOCE*: store-operated Ca2+ entry, *PLC*: phospholipase C, *TLR4*: toll-like receptor 4, *NF-kβ*: nuclear factor-kappa beta, *ROS*: *reactive oxygen species*, *ACC*: acetyl coenzyme A carboxylase, *FAS*: fatty acid synthase, *HMGC*: 3-hydroxyl-3-methylglutaryl-CoA synthase 2, *ADP*: adenosine 5′ diphosphate, *MI*: myocardial infraction, *NLRPs*: family of leucine-rich repeat containing proteins, *PPAR-α/γ*: peroxisome proliferator-activated receptor alpha/gamma, *LOX:* lipoxygenase, *PLA2*: phospholipase A2, *RANTES*: regulated upon activation, normal T-cell-expressed and presumably secreted, *MIP-2*: macrophage inflammatory protein-2, *VCAM-1*: vascular cell adhesion molecule-1, *PON2*: serum paraoxonase/arylesterase 2, *TXA*: thromboxane A, *TXB*: thromboxane B, *PDGF*: platelet-derived growth factor, *aPTT*: activated partial thromboplastin time, *PT*: prothrombin time, *CT*: closure time, *ALD*: alcoholic liver disease, *NAFLD:* non-alcoholic fatty liver disease, *CRP*: C-reactive protein, *PS*: phosphatidylserine

Advances have been made in the understanding of the mechanism of action of various fungi metabolites, but many questions remain unanswered. For the past few years, there has been an exponential growth in the field of fungi-derived medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects.

At present, most of the studies are based on in vitro research and/or animal models, while the anti-inflammatory and antithrombotic mechanism of these fungi-derived metabolites in human body by targeted trials has not yet been fully described for all fungi compounds, as well as for combinations of fungi metabolites. Therefore, the action mechanism of fungi-derived bioactives in the process of anti-inflammatory response needs to be further studied. The research on the separation process and the study of structure–activity relationship of monomer components of fungi-derived products should be built upon, as well as the putative synergistic effects of multi-targeting anti-inflammatory fungi metabolites. In the future, active components in fungi and mixtures of fungi compounds with synergistic effects can be analyzed with the help of modern research means, such as network pharmacology, modern multi-omics and metabolomics, artificial intelligence-based docking modeling molecular biology, genetics, and epigenetics, to determine the relevant anti-inflammatory response mechanism and provide a basis for the clinical application of fungi-derived metabolites.

Moreover, the library of fungi-derived anti-inflammatory and antithrombotic bioactives has dramatically been increased by the inclusion of specific plant-derived medicinal compounds efficiently biosynthesized by hundreds of endophytic fungi. Nonetheless, the exciting progress that has been made in the field of functional genomics, genome mining and genome scanning, fermentation technology, green combinatorial chemistry, and systems biology might remove the roadblocks in the way of commercial success of this innovative approach. The design of endophyte-dependent enhanced in vivo and in vitro production of plant-derived valuable metabolites is of prime importance for the pharmaceutical industries and provides a plethora of valuable compounds with future perspectives for the healthcare systems and for a "green drug revolution."

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