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REVIEW

Action Mechanisms of Medicinal Plant Components as Antimycosis: A Literature Review

Mecanismos de acción de los componentes de plantas medicinales como antimicóticos: Una revisión bibliográfica

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ABSTRACT

Mycosis poses a significant threat to global health, particularly in immune-compromised individuals, and the rise of antifungal resistance has further complicated their treatment. The rise in fungal infections (FIs) is a growing concern, contributing significantly to global morbidity and mortality rates. Medicinal plants (MPs), with their long history of use in traditional medicine, have emerged as a valuable source of bioactive compounds with potent antifungal properties. The current study explores the mechanisms by which plant active constituents (PACs) exert their antifungal effects, including inhibition of cell membrane (CM) and cell wall (CW) synthesis, mitochondrial dysfunction, the inhibition of Nucleic acids (Nas) and protein synthesis (PS), inhibiting the electron transport chain, decreasing ATP production, inhibiting glycolysis, oxidative phosphorylation, and oxygen uptake by cells, and this lead to affect cell division, protein production, and/or inhibiting its mycelial growth and spore germination. Compounds such as flavonoids, alkaloids, terpenoids, and other PACs have demonstrated significant antifungal activity through these diverse mechanisms, offering potential alternatives to conventional antifungal drugs. This study highlights the potential of MPs as a foundation for developing novel antifungal therapies. Furthermore, it underscores the importance of understanding the intraocular mechanisms of action (MsOA) to combat antifungal resistance and improve therapeutic outcomes. This comprehensive analysis not only validates the use of MPs in traditional medicine but also provides a roadmap for future research and drug development in the fight against FIs. This study aligns with and supports sustainable development goals (SDGs), including good health and well-being (SDG 3) and other goals.

Keywords: Plant Active Constituents; Mechanism of Action; Antifungal Activity; Natural Products; Sustainable Development Goals (Sdgs); Good Health and Well-Being; Innovation in Healthcare.

RESUMEN

Las micosis suponen una importante amenaza para la salud mundial, sobre todo en individuos inmunodeprimidos, y el aumento de la resistencia a los antifúngicos ha complicado aún más su tratamiento. El aumento de las infecciones fúngicas (IF) es cada vez más preocupante y contribuye significativamente a las tasas mundiales de morbilidad y mortalidad. Las plantas medicinales (MP), con su larga historia de uso en la medicina tradicional, se han revelado como una valiosa fuente de compuestos bioactivos con potentes propiedades antifúngicas. El presente estudio explora los mecanismos por los que los componentes activos de las plantas (PACs) ejercen sus efectos antifúngicos, incluyendo la inhibición de la síntesis de la membrana celular (CM) y de la pared celular (CW), la disfunción mitocondrial, la inhibición de los ácidos nucleicos (Nas) y la síntesis de proteínas (PS),

la inhibición de la cadena de transporte de electrones, la disminución de la producción de ATP, la inhibición de la glucólisis, la fosforilación oxidativa, y la captación de oxígeno por las células, y esto lleva a afectar a la división celular, la producción de proteínas, y/o inhibir su crecimiento micelial y la germinación de esporas. Compuestos como los flavonoides, alcaloides, terpenoides y otros PACs han demostrado una importante actividad antifúngica a través de estos diversos mecanismos, ofreciendo alternativas potenciales a los fármacos antifúngicos convencionales. Este estudio pone de relieve el potencial de los MP como base para el desarrollo de nuevas terapias antifúngicas. Además, subraya la importancia de comprender los mecanismos de acción intraoculares (MsOA) para combatir la resistencia a los antifúngicos y mejorar los resultados terapéuticos. Este análisis exhaustivo no sólo valida el uso de MP en la medicina tradicional, sino que también proporciona una hoja de ruta para futuras investigaciones y desarrollo de fármacos en la lucha contra los IF. Este estudio se alinea con los Objetivos de Desarrollo Sostenible (ODS) y los apoya, entre ellos el de buena salud y bienestar (ODS 3).

Palabras clave: Constituyentes Activos Vegetales; Mecanismo de Acción; Actividad Antifúngica; Productos Naturales; Objetivos de Desarrollo Sostenible (ODS); Buena Salud y Bienestar; Innovación en Sanidad.

INTRODUCTION

Fungal infections (FIs) are a major health concern for people, and it is estimated that more than 1,5 million people die each year due to fungal diseases worldwide. FIs are a significant problem in the medical field due to increasing resistance, which has made antifungal drugs more challenging to treat these infections.[1] Mycoses are classified medically into different categories according to acquisition route, degree, site of infection, and virulence. According to the degree and type of tissue involvement, they are divided into systemic, subcutaneous, cutaneous, and superficial mycosis.[2]

Mycosis cases increase day by day, it causes high rates of illness and mortality. The prevalence of increased medication resistance for fungal illnesses and related sequelae is extremely essential, even as novel fungus species are emerging. Antifungal drugs have several drawbacks, such as decreased fungistatic activity, elevated toxicity, and renal failure.[3] In the future, finding new medicines that could be an effective alternative therapy for the majority of mycosis is crucial, especially for the treatment of opportunistic mycosis,[4] that are more effective than the available conventional drugs.[5] With a long history of usage in traditional medicine, plants have become a promising source of bioactive chemicals with antimycotic activities. However, the limitations of natural compounds may be overcome by the variety of chemical structures and modes of action.[6] The best defences against disease and their prevention issues are substances or compounds derived from natural origins because they are mainly safe and available in nature. Thus, we can state that the usage of natural products, especially plants, is an alternative way to overcome mycosis.[7] PACs of Plants have been found to possess potent antifungal activity. PACs are natural active compounds derived from plants that possess therapeutic properties.[8] These compounds have been used to treat various ailments, including FIs. Many PACs have been shown to inhibit fungal growth by targeting different MsOA. PACs such as alkaloids, flavonoids, terpenoids, and phenolic compounds have been found to possess antifungal properties.[4] These compounds have diverse and complex MsOA, on the other side, understanding their mode of action is essential for the development of effective antifungal therapies according to the identification of specific intracellular or molecular targets and pathways affected by PACs, which can guide the development of novel antifungal agents (AAs) with improved efficacy and reduced toxicity[9,10] so that PACs offers a potential solution to combat resistant fungal strains via their diverse MsOA.[11] Furthermore, it enables the identification of specific molecular targets and pathways of PACs, which can guide the development of novel AAs with improved efficacy and reduced toxicity.[6] The MP active antifungal components article aligns and supports sustainable development goals (SDGs) by improving good health and well-being, supporting responsible consumption and production, improving life on land, fostering industry, innovation, and infrastructure, and encouraging global partnerships for goals.

To ensure a particular medical or unique antifungal property for fungal disease problems to optimize the efficiency, dosages, and delivery methods for FIs that achieve sustainability, bioavailability, and potential for large-scale production for the new natural products. Therefore, the objective of this study will be to delve into the mechanisms by which MPs exert their antifungal effects, highlighting their potential as novel therapeutic agents. Examining the molecular and cellular pathways targeted by PACs, moreover, provides a comprehensive understanding of their efficacy and underscores the importance of integrating traditional knowledge with contemporary scientific methods in the fight against FIs and their potential as AAs or provides an overview of the mechanism of action (MOA) of PACs as antifungals.

Mycosis and targets of antifungal medications

Fungi are ubiquitous in distribution and can cause a range of mycotic infections, from mild skin infections to

life-threatening systemic infections in hosts.[12] Mycosis can affect various parts of the body, involving nails, hair, and skin, as well as systemic organs. However, AAs are medications used to treat mycosis by killing or inhibiting the growth of fungi.[13] In these issues, researchers looked at a variety of medicines, both synthetic and natural, as well as the possible relationships between the antifungal mechanisms and the many facets of fungal growth, metabolism, or virulence. One possible method of reducing growth in harmful fungal strains is to interfere with their metabolic pathways by compromising their cell wall (CW) or mitochondrial function. Similarly, one of the antifungal tactics may involve interfering with fungal efflux pumps, ergosterol syntheses, or the Hsp90 protein in order to reduce the fungal capacity to develop resistance to antimicrobial medication. Furthermore, antifungal tactics may focus on interacting with biofilms' intricate structure. Antibiofilm characteristics are associated with the thickness of the extracellular matrix and its constituents, including efflux pumps, and the yeast's capacity to create pseudohyphae, besides their effect on fungal cell viability and biofilm biomass. Similarly, the morphological impact of other fungal pathogens could be employed, besides yeast hyphae development.[4,14]

Today, there are just a few kinds of antifungal drugs accessible since it is difficult to target these eukaryotic microbes without affecting animals or humans. Some common medical AAs include Azoles, Polyenes, Allylamines, pyrimidine analogs, echinocandins, and other antibiotics.[13] These antifungals target the primary distinctions between human/animal and fungal cells, such as the composition of the CW and plasma membrane, the manufacture of ergosterol, or the disruption of RNA or DNA synthesis in a way particular to a given fungus.[15,16] Finding novel antifungal compounds with new MsOA is essential to combating human pathogenic mycosis due to the scarcity of licensed fungicides or fungistatic and the dramatic rise of multi-antifungal resistance.[16]

Studying the antifungal MOA has many purposes, including understanding its efficacy and selectivity, combating drug resistance, developing novel antifungals, optimizing treatment strategies, minimizing side effects, and addressing emerging infections.[5,17,18,19] Listing the MOA of antifungal drugs helps the understanding of natural products and active compounds' actions.[20]

Generally, the mechanism of antimicrobial (bacteria and fungi) target and action based on the function included disruption of the fungal CW, inhibition of CM synthesis, inhibition of protein function and protein synthesis, interference of nucleic acid synthesis, inhibition of microbial metabolic pathways, and folate metabolism.[21]

Most antifungal medication MsOA target CMs, CWs, and fungal nucleic acid synthesis. Antifungal drugs can be grouped into five classes based on their pathway/MOA: azoles and allylamines, which inhibit the synthesis or production of ergosterol (instead of human sterols); polyenes, which combined with mycotic ergosterols physicochemically; echinocandins, target the fungal cell-wall complex ß (1-3)-glucan synthase and pyrimidines or 5-fluorocytosine (5FC), which activated by fungal intracellular and alters the formation of nucleotide subunits. The development of antimycotic resistance is caused by a variety of mechanisms, including changes in drug targets, modifications to ergosterols biosynthesis, decreases in the intercellular concentration of target enzymes, and overexpression of the antifungal medication target.[17,22]

In clinical practice, only four kinds of systemic antimycotic medications are now used: polyenes, echinocandins, azoles, and pyrimidines. Azoles class antifungal drugs, first reported during 1960s, work by inhibiting the synthesis or production of ergosterol (fungal CM's vital component), and the fungal cell's permeability increases, resulting in its demise. The primary molecular pathway target of azole is the enzyme (cytochrome P-450) Erg11p/Cyp51p.[23] Class Echinocandin antifungals were discovered and reported in the late 1900s. It acts on beta (1,3)-glucan (it is unique to fungi), a crucial component of the fungal CW that is required for its integrity and stability.[24] Class Polyene antifungals were discovered in the 1950s, which act to attach with ergosterol (it is unique to fungal CMs), causing altered permeability and may cause membrane disruption.[23,25] Analog Pyrimidine antifungals inhibit NAs biosynthesis. The most common analog is 5-FC (Flucytosine), which interferes with pyrimidine bases metabolism in RNA and DNA in addition to interfering PS. 5-FC is converted to 5-FU (5-fluorouracil), then by UMP pyrophosphorylase to FUMP (5-fluorouridylic acids), after that phosphorylated and integrated into RNA, causing protein production to be disrupted. Moreover, 5-FU is transformed to 5-FDUMP (Five-fluoro-deoxyuridine mono-phosphate), a strong inhibitor of thymidylate synthase, which is important in DNA synthesis as well as nuclear division. Despite this complex mechanism, 5-FC is not used alone but used combined with another antifungal like amphotericin.[23,26]

But new antifungal classes have been in late-stage clinical trials, for instance, olorofim and fosmanogepix as novel dihydroorotate dehydrogenase and Gwt1 enzyme inhibitors respectively.[27,28,29] Fosfomanogepix and Olorofim represent two innovative AAs with distinct MsOA. Fosfomanogepix, through its active form manogepix, targets the fungal enzyme Gwt1, disrupting the maturation of GPI-anchored proteins essential for fungal CW integrity and host adhesion. On the other hand, Olorofim, an orotomide, inhibits the fungal dihydroorotate dehydrogenase (DHODH), impairing pyrimidine biosynthesis and fungal proliferation. While Fosfomanogepix exhibits broad potential by affecting fungal cell structure, Olorofim demonstrates specificity against molds and dimorphic fungi, highlighting its niche but significant clinical utility. Together, these agents underscore the advancement in antifungal drug development, offering targeted therapies with reduced cross-reactivity and toxicity, paving the way for improved treatment strategies against resistant and invasive FIs.[30,31,32,33,34,35] Fosfomanogepix (manogepix active form) inhibits GPI-anchored mannoproteins, affecting fungal CWs/CMs. Orotomides (Olorofim) inhibit

pyrimidine biosynthesis, which affects fungal proliferation.[23]

Another mode of action of antifungal drugs used, including phenylmorpholines, of which amorolfine is the only human therapeutic representative, works by influencing Erg24p (delta 14 reductase) and Erg2p (delta 8–delta 7 isomerase), two targets in the ergosterol pathway. The fungal translation EF2 (elongation factor two) is blocked by the sordarins class, which inhibits PS. Zofimarin, BE31045, SCH57504, xylarin, hypoxysordarin, and GR135402 are further protein inhibitors. Novel targets were investigated in order to address the issues brought on by the overuse of three classes polyenes, azole, and echinocandins. Using inhibitors such as myristate and histidine analogues or myristoylpeptide derivatives, quinolines, aminobenzothiazoles, and benzofurans, proposed antifungal medications have been designed to target possible targets such as the N-myristylation of fungal proteins. Another possible target is the polymerisation of CW polysaccharides from uridine di-phospho sugars.[36]

Bioactive Plant components

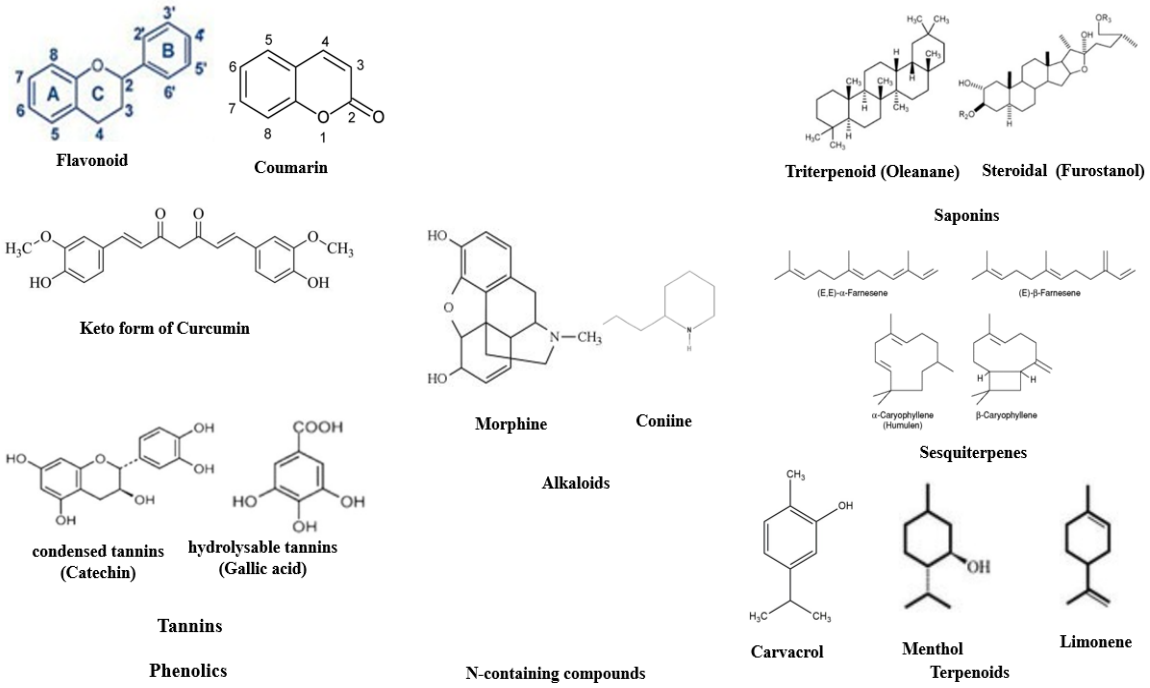

Figure 1. Classes of plant active components example

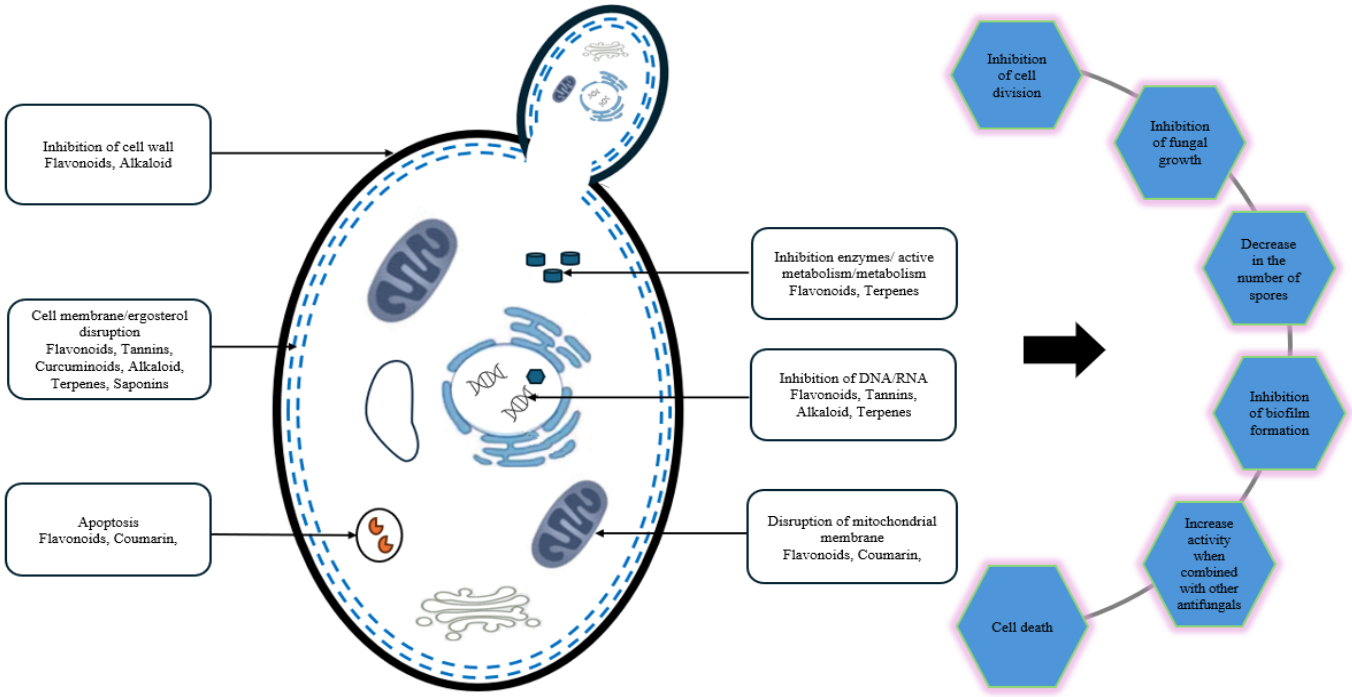

Figure 2. Mechanisms of action of plant active constituents diagram

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NPCs and products contain a variety of chemical compounds that support plant growth and development. These resources from primary metabolites are needed for plant activities including respiration, translocation, and photosynthesis. According to estimates, about 35 000 species of chemical compounds are used globally for therapeutic purposes.[37] Numerous chemicals have been recorded in crops and other plants. Several economically significant molecules are included in these metabolites, including antimicrobials, pigments, poisons, enzyme inhibitors, immunomodulatory agents, receptor agonists and antagonists, insecticides, anticancer agents, and elicitors in plants and animals.[37,38]

Secondary metabolites (SMs) are the naturally occurring compounds produced from principal metabolites but are not directly related to growth and development. These are typically the result of biosynthetic changes, for example, methylation, hydroxylation, glycosylation, or the byproduct of primary metabolites. SMs are definitely more complex than primary metabolites in terms of side chains and structural characteristics[39] (figure 1).

Based on the biosynthesis route, there are three primary types of plant metabolites: (1) phenolic groups, which are made up of sugar and benzene rings; (2) terpenes and steroids, which are mostly made up of carbon and hydrogen; and (3) molecules that contain nitrogen. The main Phenolic compounds include coumarin, furanocoumarins, Lignin, flavonoids, isoflavonoids, and tanins. Also, the main N-containing compounds include Alkaloids cyanogenic glucosides, and non-protein amino acids. The main terpenes compounds include Monoterpenes, sesquiterpenes, di, tri, tetra, and poly-terpenes.[37,39]

There have been numerous reports of metabolites from plants and other natural sources inhibiting pathogenic fungi. Several categories of PACs have antifungal activity, including saponins, terpenoids, coumarins, phenolic compounds, essential oils, alkaloids, and peptides.[40]

Phenolic compounds are aromatic chemicals produced by either the shikimic acid (SA) pathway or the mevalonic system, whereas terpenes are produced from the precursor acetyl-CoA via the mevalonic process. SMs that contain nitrogen, like alkaloids, are mostly made from aromatic acids from the SA-pathway or aliphatic amino acids from the tricarboxilic acid pathway by the use of acetyl-CoA and mevalonic acid. The pharmaceutical industry has made extensive use of these three kinds of metabolites.[37,41]

In the same context, alkaloids, isoprenoids, saponins, glycosides, phenolic compounds, and other groups encompass a wide range of individual compounds, ranging from a few to hundreds or even thousands. The chemical structure of these metabolites dictates their specific biological functions. For instance, plants produce SMs to defend against pathogens or to detoxify harmful byproducts of primary metabolism. Notably, certain secondary compounds significantly influence the nutritional and sensory properties of PACs. The ability of plants to synthesize diverse multifunctional organic compounds with varied properties enables their use in numerous applications, including body care products, immune system support, medicinal uses (e.g., as analgesics, antioxidants, or blood pressure regulators), dietary supplements, bioindicators, and more.[42]

Antimycotic medicinal PACs and their mechanism of Action (MOA)

All inhibition mechanisms/pathways of the FI include the inhibition or decrease in action mechanisms of antifungal intracellularly, fungal virulence, and fungal interactions (biofilm formation or quorum sensing) as well as overcoming antifungal resistance.[14,17,43,44,45,46]

Among the antimycotic pathways of plant SMs are (a) reducing the number of spores and hyphal growth; (b) altering DNA replication and disrupting the cell cycle; (c) preventing ergosterol (fungal membrane sterols) synthesis, disrupting CM permeability, and encouraging the destruction and lysis of CWs; (d) inhibiting the synthesis of fungal mycotoxin; and (e) preventing the formation of fungal biofilms and destroying existing ones,[47,48] (figure 2).

Phenolics

Flavonoids and related class

Flavonoids are SMs that are mostly found in plants and are classified as a wide types of polyphenols. Foods including chocolate, onions, apples, bananas, grapes, berries, red wine, sea buckthorns, and all citrus fruits are rich in these natural compounds, as are drinks like red wine, cider, green tea, black tea, and oolong tea.[49,50] Their wide flavonoid structure consists of a 15-C skeleton made up of double phenyl rings joined by a 3-carbonated heterocyclic ring (C6-C3-C6). The following subclasses can be distinguished based on the modifications in the central carbon ring: flavanones, flavonols, flavones, anthocyanidins, and isoflavones.[49]

Flavonoids, a class of PACs, have numerous beneficial effects on human health. Thus, identifying flavonoids that exhibit antifungal properties at low concentrations or in synergistic combinations could provide a promising solution to the challenges posed by fungal as well as bacterial infection. Combining flavonoids with existing antifungal drugs offers a strategic approach to minimizing side effects and reducing toxicity, thereby enhancing therapeutic outcomes.[4,51]

The antifungal properties of flavonoids work by interfering with mycotic CM integrity, disrupting ergosterol synthesis, and altering important signal transduction pathways, eventually delaying fungal growth and

pathogenicity.[52] Also, include membrane interruption, CW biosynthesis inhibition and cell division stopping, mitochondrial dysfunction, and the inhibition of NAs and PS.[53]

Baicalein (*Scutellaria baicalensis* plant isolate) demonstrated anti-Candida action by causing intracellular chemical efflux and CM structural deformation.[54,55] According to Dai et al.[56] Baicalein caused apoptosis via impairing mitochondrial membrane function and raising intracellular ROS (reactive oxygen species) levels. According to Kang et al.[57] and Savu et al.[55] the flavonoid's antifungal activity against strains of *C. krusei* is linked to the disruption of mitochondrial homeostasis rather than intracellular ROS production or apoptosis. The primary mechanism of baicalein-inhibited *C. albicans* biofilms is associated with cell surface hydrophobicity and mRNA expression decrease.[55,58] Important anti-virulence and antibiofilm properties are present in both natural and synthesized flavonoids, raising expectations for the future development of potent anti-Candida treatments.[55]

Numerous flavonoids have been studied for their antifungal properties, demonstrating potential as effective, affordable, and promising agents for combating FIs. These compounds inhibit fungal growth through multiple mechanisms, such as disrupting the plasma membrane, inducing mitochondrial dysfunction, and interfering with CW synthesis, cell division, protein production, and efflux pump activity. Flavonoids also show significant potential in synergistic combination therapies with existing antifungal drugs, offering a more effective and supportive approach to developing innovative treatments against fungal pathogens.[4]

Fungal cells' mitochondrial activity is disrupted by flavonoids, which lowers energy production and eventually causes cell death. Although the exact processes by which flavonoids cause malfunction of the fungal mitochondria are still fully unknown, the following theories have been put forth: causing the depolarisation of the mitochondrial membrane and blocking electron transport chain complexes. The complexes of the electron transport chain, which produce ATP by oxidative phosphorylation, can be inhibited by flavonoids. Reactive oxygen species buildup and a reduction in ATP synthesis may result from this, which could oxidatively damage DNA, proteins, and mitochondrial membranes. Additionally, flavonoid phenolic compounds have the ability to depolarise the mitochondria by upsetting the electrochemical gradient across the inner membrane. This may lead to a reduction in ATP synthesis and cytochrome c release, which may trigger apoptotic pathways and induce fungal cell death.[59]

Other PACs interfere with the structure or function of the plasma membrane, such as Catechin (flavan-3-ol), which belongs to the subgroup of the polyphenols group named flavonoids. Epigallocatechin gallate (EGCG, epigallocatechin-3-gallate) is the ester of gallic acid and epigallocatechin and is a type of catechin. Polyphenols derived from green tea, such as EGCG, impair the fluidity and permeability of the fungal CM by interacting with ergosterol, a major component of fungal membranes. Epigallocatechin gallate can inhibit a variety of clinically isolated yeasts, including *Candida* sp. by inhibiting the activity of dihydrofolate reductase.[23,60,61]

EGCG indirectly disrupts the ergosterol mycotic biosynthetic pathway by interfering with the folate cycle and inhibiting sterol C-24 methyltransferase, which reduces the cellular pool of S-adenosyl-methionine. The electron microscopy studies have revealed that treatment with EGCG causes structural deformities in *C. albicans* cells, including CW damage and the release of cellular contents. Additionally, molecular docking experiments have demonstrated that EGCG exhibits strong binding interactions with ergosterol, a key component of the mycotic CM.[62] Combining azole antifungal treatments with EGCG could potentially lower the required dosage of conventional AAs by triggering apoptosis in fungal cells. This approach may help mitigate adverse side effects and reduce the risk of drug-resistant strains developing. However, further research is necessary to fully explore and validate this strategy.[23,61]

The cause of flavonoid activity

According to the lipophilicity evaluation, the lipophilic nature of the flavonoids in membranes was mostly responsible for their permeabilization capacity, leading to altered permeability. Given their lipophilic nature, flavonoids are thought to passively diffuse across the CM in their undissociated form, disrupting the membrane's structure and potentially acidifying the cytoplasm, allowing DNA (or RNA), proteins, and inorganic ions like potassium or phosphate to leak out of the cell.[63,64]

Flavonoids inhibit fungi primarily due to their chemical structure, which includes multiple hydroxyl (-OH) groups, conjugated double bonds, and aromatic rings. These features enable flavonoids to disrupt fungal CMs by binding to ergosterol, a key component of fungal membranes, leading to increased permeability and cell leakage.[65] Additionally, flavonoids can inhibit fungal enzymes such as chitin synthase and 1,3-beta-glucan synthase, which are essential for CW synthesis, weakening the structural integrity of fungal cells.[66] Their ability to generate reactive oxygen species (ROS) further damages fungal cellular components, including DNA, proteins, and lipids, contributing to antifungal activity.[67]

Coumarin

Class Coumarin (2H-1-benzopyran-2-one) is a therapeutic compound that occurs naturally as a secondary active metabolite in plants, bacteria, fungi, and essential oils and can also be produced through chemical

synthesis. It has been extracted from various plant families, including Clusiaceae, Umbelliferae, and Rutaceae.[68] To date, over 1300 coumarins have been detected in fungi, bacteria, and commonly in plants. Multicellular and unicellular fungi have played a significant role in inspiring the synthesis of chemically diverse drugs derived from natural sources.[69]

Certain simple and intriguing chemical structures demonstrate antifungal properties and may share similarities with coumarins in terms of their activity. These structures could serve as a basis for further exploration in antifungal drug development. Beside natural coumarins, other natural products with relatively simple structures, such as sarisan and certain coumarin derivatives, also exhibit notable biological activities. These compounds, despite their structural simplicity, demonstrate potential in various therapeutic applications, including antifungal properties, and warrant further investigation for their pharmacological potential.[70,71]

Cell biological and biochemical investigations on the coumarin objectives have resulted in an in-depth knowledge of cellular behaviour toward this interesting nucleus. Based on additional research, synthetic alteration of the parent compounds of coumarins has produced new molecules with enhanced biological potential and activity. In the current part, coumarin derivatives and their potential antifungal activities have been introduced.[71]

The MsOA of coumarins are highly complex and not yet fully understood. Nevertheless, they can generally be categorized into two processes: light-dependence and light-independence. While extensive research has already been conducted on the light-dependent effects of furanocoumarins and coumarins, additional investigations are needed to elucidate the light-independent mechanisms and their broader biological implications.[71,72,73,74] Exposure to coumarin for 24 hours has been shown to disrupt the CM and CW of *C. albicans*, leading to a reduction in cytoplasmic volume and causing structural disorganization. However, the precise MOA of coumarin (1,2-benzopyrone) remains unclear and requires further investigation to be fully understood.[75] While Coumarin reduced drastically the protein and carbohydrate contents of the cytoplasm (transport of Metabolites) of the genus *Pythium* as parasitic oomycetes.[76]

Effects of coumarin on other cells

Coumarins have been found to inhibit the phosphorylation process. For instance, imperatorin, a furanocoumarin derived from *Imperatoria ostruthium* and *Ammi majus*, has been shown to suppress both respiration and phosphorylation in isolated liver mitochondria when succinate is present. This highlights the potential of coumarins to interfere with critical cellular energy processes.[77] Coumarin's natural compound and some of its derivatives inhibited glycolysis, oxidative phosphorylation, and oxygen uptake by cells.[78,79]

Coumarin and its derivatives exert multiple biological effects, including the induction of cell apoptosis, targeting of the PI3K/Akt/mTOR signaling pathways, inhibition of carbonic anhydrase, and disruption of microtubule function. They also play a role in inhibiting tumor multidrug resistance, suppressing angiogenesis, and modulating ROS. Derivatives of coumarins exhibit anti-migratory, anti-invasive, and antiproliferative properties by arresting the cell cycle and promoting apoptosis. These activities highlight their potential as therapeutic agents in various diseases, including cancer.[80]

Coumarin has been shown to reduce the mitochondrial eukaryotic membrane possibility, trigger the release of CytC (cytochrome c), and activate caspase-3, ultimately guiding apoptosis. These findings shed light on the mechanisms through which coumarin causes the cell cycle to stop and apoptosis in HeLa cells (human cervical cancer), providing valuable insights into its potential as an anticancer agent.[81]

Coumarin reduces oxygen uptake by inducing structural changes in the mitochondrial matrix, causing it to become denser. Additionally, protrusions in the mitochondrial membranes become visible, accompanied by hypertrophy, indicating significant alterations in both the structure and function of these organelles. These changes highlight the impact of coumarin on mitochondrial physiology.[79]

Dermatophytes are more sensitive to coumarins than other filamentous fungi or yeasts isolated from skin infections. However, both natural and synthetic coumarins have been shown to inhibit key enzymes involved in DNA metabolism, highlighting their potential applications as antiretroviral and antitumoral agents. Further research is needed to elucidate their antifungal mechanisms and treatment capability.[82,83]

DNA gyrase, a target enzyme in certain prokaryotic bacteria such as *Staphylococcus aureus* and *E coli*, serves as the primary target for aminocoumarins. These compounds exert their MOA by inhibiting DNA gyrase, thereby disrupting bacterial DNA replication and providing a basis for their antibacterial activity.[84]

The cause of coumarin activity

Coumarins exhibit antifungal activity primarily due to their chemical structure, which allows them to interact with key cellular components and processes in fungi. The antifungal activity of coumarins is attributed to their ability to disrupt mycotic cellular membranes, inhibit essential enzymes, induce oxidative stress, and interfere with ergosterol biosynthesis. In addition, Coumarin caused mitochondrial Ca^{2+}-dependent apoptosis in yeasts. These mechanisms are facilitated by their planar, lipophilic structure and functional groups, which allow them

to target multiple cellular processes in fungi. The references provided highlight the scientific basis for these mechanisms, demonstrating the potential of coumarins as effective AAs. The unique chemical structure and physical characteristics of its 2H-chromen-2-one (aromatic ring and lipophilic) ring or oxaheterocyclic ring, which facilitates simple binding to a variety of bioactive components of fungal cells, are what determine coumarin action. Coumarins possess a planar structure with conjugated double bonds, which enables them to intercalate into fungal CMs and disrupt their integrity. Their lipophilic nature allows them to penetrate the lipid content of two phospholipid layers of mycotic cells, indicating membrane destabilization and leakage of cellular contents.[85,86,87]

Tannins

Compounds known as tannins (according to structures classified into three groups: hydrolysable, complex, and condensed tannins) are a class of SMs that are present in plants. They function as first-line defences against invasive infections and are polyphenolic in origin. Numerous investigations have illustrated the various functions of tannins, emphasising their efficacy as all-purpose antimicrobial substances. Because they limit the formation of NAs and stop enzymatic activity, tannins have antiviral, antifungal, and antibacterial properties. Furthermore, the main function of tannins is to fortify the plant CW, rendering it nearly impervious to dangerous diseases.[88]

Tannins acted by inhibiting active hyphal growth of molds and spore germination of *Penicillium digitatum*. The integrity of the mycotic CW and the CM permeability are the suggested antifungal mechanism of tannins on *P. digitatum*. Intracellular materials like sugars leaked out as a result of the CW and plasma membrane being disrupted. According to these results, tannins attack the *Penicillium* mold CW.[89]

Tannic acid exerts its antimycotic activity against yeast *Candida* spp. and affects Candidal biofilm formation. Its MsOA can be related to the stimulation of signals that result in apoptosis in mycotic cells,[90] or it may inhibit quorum sensing.[91]

Punicalagin (a member of the tannin class and isolated from pomegranate fruit) is a potent yeast DNA topoisomerases (I and II) inhibitor. Punicalagin may be an innovative medicinal substance that warrants more investigation. Considering the previously documented ability of punicalagin to block one of the main common enzymes named squalene epoxidase, used in the biosynthesis of membrane ergosterol.[92] This is marked as punicalagin as an encouraging AA because of its multiple targets inhibition mechanisms.[93]

The cause of tannins activity

Tannins inhibit fungi due to their polyphenolic structure, characterized by multiple hydroxyl (OH) groups and aromatic rings, which enable them to form strong hydrogen bonds and hydrophobic interactions with fungal cellular components. They disrupt fungal CMs by binding to proteins and lipids, leading to membrane destabilization and increased permeability.[94] Tannins also inhibit key fungal enzymes, such as those involved in CW synthesis and energy metabolism, by forming complexes with their active sites.[95] Additionally, their ability to chelate metal ions essential for fungal growth further contributes to their antifungal activity.[96]

Other phenolic compounds effect might be ascribed to changes in mycotic cell permeability of the membrane,[97] in addition to the activation of defence mechanisms in the host.[98]

Curcuminoids

Curcumin is a diarylheptanoid (1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione) belonging to the group of curcuminoids, which are phenolic pigments accountable for the yellow color pigment of turmeric.[99] Curcuminoids are the major polyphenolic compounds found in turmeric rhizomes. The curcuminoids include curcumin (the main bioactive component), demethoxycurcumin, and bisdemethoxycurcumin. The unique structure of curcumin has phenolic hydroxyl groups, heptadiene chain, and a diketone moiety.[100]

The binding to mycotic membrane ergosterol might be the MOA of curcumin against yeast, including *Candida* membrane disruption.[101,102]

PACs can also target intracellular organelles such as mitochondria or nuclei. For example, berberine derived from *Berberis vulgaris* inhibits mitochondrial respiration by interfering with electron transport chain complexes I and III. Similarly, curcumin derived from Curcuma longa inhibits fungal growth by inducing oxidative stress and DNA damage in the fungal nucleus.[103,104,105]

The antifungal effect of *Curcuma longa,* containing curdione, curcumenol, curzerene, isocurcumenol, curcumin, ß-elemene, curcumol, and germacrone active compounds against several molds included mycotic CM disruption and inhibition of mycotic ergosterol synthesis, succinate dehydrogenase, respiration, and NADH oxidase.[106]

The cause of curcuminoids activity

Curcuminoids, including curcumin, inhibit fungi due to their unique chemical structure featuring ß-diketone groups, aromatic rings, and hydroxyl groups. These structural elements enable curcuminoids to disrupt fungal

CMs by binding to ergosterol, increasing membrane permeability, and causing cell leakage.[107] They also generate ROS, which damages fungal cellular components such as DNA, proteins, and lipids.[108] Additionally, curcuminoids inhibit key mycotic enzymes, including chitin synthase and 1,3-beta-glucan synthase, essential for CW integrity.[109]

N-containing compounds

Nitrogen-containing secondary metabolites (NCSM) include cyanogenic glycosides (CNGs), alkaloids, and nonprotein amino acids. An aglycone with a sugar group attached makes up CNGs, glycosides containing α-hydroxynitrile. Although the compounds themselves are not poisonous, CNGs have the potential to be extremely dangerous molecules that, when hydrolysed, release hydrogen cyanide, which can cause acute cyanide poisoning.[110]

Non-protein amino acids-NCSM, which constitute significant nitrogen reserves in plants, are another group of nitrogenous molecules found in plants. Non-protein amino acids-NCSM mainly aid plants in fending off dangerous insects, besides other active properties, including antimycotic, antibacterial, and anticancer.[111]

Alkaloid

Alkaloids are organic compounds arising NPCs that are a part of the base class and include nitrogen. The suffix "-ine," which indicates that they are amine-like chemicals, usually appears at the end of their names. Both humans and other animals can experience a variety of noteworthy physiological consequences from alkaloids. Morphine, strychnine, quinine, ephedrine, and nicotine are a few well-known examples. In terms of structure, alkaloids frequently have one or more nitrogen atoms integrated into a cyclic structure, which is a ring system. The majority of alkaloids are crystalline solids that are colourless and nonvolatile when they are pure.[112]

More than twenty percent of plant species contain alkaloids, which are typically acquired in high quantities in different families of plants, for example, the Rutaceae, Solanaceae, Apocynaceae, Fabaceae, Polygonaceae, and Papaveraceae. The classification of alkaloids based on their chemical structure includes, among others, pyridine, indole, isoquinoline, scopolamine, and organic amine alkaloids.[113] Alkaloids possess diverse biochemical active properties and are utilized in the treatment of various conditions, including microbial diseases, dementia, cancer, and reliefe pain. They serve as a significant source for the enhancement of numerous therapeutic drugs.[114]

It has been demonstrated that alkaloids exhibit antifungal action against a variety of yeast and mould fungi, including dermatophytes and *Candida* species. Alkaloids break down the fungal CM to produce their antifungal effects. They accomplish this by attaching themselves to ergosterol and other membrane constituents, which causes the membrane to rupture and leak.[115]

Berberine (BBR), an alkaloid found in various medicinal plants, including *Hydrastis canadensis*, *Coptis chinensis*, and *Berberis vulgaris*, has a long history of use in folk medicine. Recently, the combination of flucytosine and BBR has shown significant effectiveness in eliminating flucytosine-resistant *C. albicans*.[116,117]

Berberine, an isoquinoline alkaloid, exhibits antioxidant properties by inhibiting the generation of free radicals (ROS) and enhancing the activity of antioxidant enzymes. Furthermore, it affects the function of mitochondria by reducing O_2 respiration and boosting the membrane of mitochondria potential, thereby protecting against oxidative damage.[118]

Berberine induces changes to the integrity of plasma and mitochondrial membranes, potentially targeting specific sites close to cellular DNA, which results in apoptotic cell death. Additionally, berberine has been shown to decrease the viability of biofilms formed by fluconazole-resistant yeast *Candida tropicalis* in laboratory conditions.[119] Berberine holds promising therapeutic potential as an AA or as a key active ingredient in antimycotic medications, particularly for combating biofilm infections linked to antifungal resistance. It has been shown to effectively reduce the viability of *Candida* spp. biofilm, prevent their formation, and substantially interrupt their spatial structures.[120]

The methanolic extract derived from the roots and leaves of *M. communis* demonstrated significant antifungal activity against *Candida glabrata*. Scanning electron microscopy revealed that the extract likely targets the CW and CM of *Candida* cells, ultimately causing cell death. These findings suggest that the methanolic extracts of *M. communis* roots and leaves could be valuable sources for developing herbal-based treatments against *Candida glabrata*.[121]

Alkaloids derived from *H. rhamnoides* (sea buckthorn), such as 4-quinolone, fluoroquinolone, and acridone, inhibit fungal growth by downregulation of the *ICL1* expression gene in *Candida albicans*. Similarly, magnoflorine, found in *Acorus calamus*, *Celastrus paniculatus*, and *Tinospora cordifolia*, exhibits antifungal properties by suppressing α-glucosidase activity and reducing yeast *Candida albicans* biofilm formation.[122,123]

Magnoflorine (a popular alkaloid with an aporphine structure, also labeled escholine and thalictrine) can also disrupt the mycotic membrane of *T. rubrum*, leading to increased leakage of mycotic DNA or RNA. Additionally, it reduces the activity of key enzymes such as 14-α-lanosterol demethylase and squalene epoxidase, involving ergosterol syntheses pathway, thereby decreasing the mold ergosterol concentration.[124]

Berberine (quaternary benzylisoquinoline natural plants alkaloid) extracted from *Phellodendron chinense*, and *Coptis chinensis,* exhibits antimycotic activity against *Candida albicans* yeast by upregulating key genes (*ssk2*, *sln1*, *pbs2*, and *hog1*) expression and promoting the accumulation of ROS. It also inhibits chitin synthase gene (*chs3*) expression and gene ß-(1,3)-glucan synthase (*gsc1*), leading to damage in cytoplasmic integrity, suppression of germ tube and hyphae formation, and disruption of the CW structure.[125]

Berberine (natural alkaloid) also demonstrated cooperative effects (*in vivo* synergism) when used in combination with amphotericin or flucytosine as AAs. Specifically, when combined or paired with amphotericin antifungal in in vivo experiments, it extended the duration of mice survival suffering from yeast *Candida albicans* disseminated infections.[38,116]

The cause of alkaloid activity

Alkaloids inhibit fungi due to their nitrogen-containing heterocyclic structures, which enable them to interact with fungal cellular components. They disrupt fungal CMs by binding to ergosterol because of high alkaloid lipophilicity, increasing membrane permeability, and causing mycotic cell leakage.[126] Alkaloids also inhibit key fungal enzymes, such as chitin synthase and 1,3-beta-glucan synthase (one of mycotic CW components), weakening fungal structural integrity.[127] Additionally, some heterocyclic alkaloids may interact with fungal enzymes and some intracular macromolecules, leading to the damage of mycotic nucleic acid, proteins, and lipids.[128]

Terpenes

Terpenoids are synthesized from multiple 5-carbon units known as isoprene units. Based on their chemical structure, terpenoids are classified into various classes, including hemiterpenoids, monoterpenoids, sesquiterpenoids, diterpenoids, iridoids, sesterterpenoids, triterpenoids, and polyterpenoids.[129] Terpenes represent a large and diverse group of naturally occurring compounds widely present in plants. The phenolic -OH group plays a critical role in the antifungal properties of terpenoids, primarily by disrupting the integrity of the CM.[130]

Carvacrol and other terpenoid phenols are key ingredients in oregano and other essential oils in plants. These substances exhibit potent antimycotic properties in contrast to a variety of infections, such as yeast *C. albicans*.[131]

The strong antifungal activity demonstrated by terpenes highlights their potential as medicinal agents for the treatment of FIs. Through a variety of methods, including rupturing fungal CMs, obstructing the manufacture of fungal CWs, blocking fungal enzymes, and modifying fungal gene expression, they produce their antifungal effects. Leveraging these antifungal pathways' therapeutic potential and creating novel antifungal medicines require a deeper comprehension of them.[132,133]

The mechanistic response of fungal cells to carvacrol and related terpenoids revealed temporal changes in metabolic process, cytosolic and vacuolar pH, and calcium ion (Ca^{2+}) transients, particularly dose-dependent Ca^{2+} bursts that were linked to antifungal effectiveness. This suggests that the antifungal action involves certain signalling pathways being activated following cellular interaction with natural plant carvacrol, instead of a nonspecific disruption of mycotic membranes.[131]

Sesquiterpenes exhibit broad-spectrum antifungal activity through non-specific and specific mechanisms. One of their non-specific targets is the fungal cytoplasmic membrane. In linear sesquiterpenes, the oxidation of -OH active groups into -CHO groups reduces their effectiveness against molds. However, the addition of lactone moiety enhances their antifungal action. Methylene lactone moieties can open to form Michael-type adducts with fungal amino acids and ribo-NAs. Additionally, furanone moieties, in which metal ions are present, biosynthesis ROS, leading to strands of DNA breaks and the arising of 8-hydroxy-2'-deoxyguanosine in fungal nucleic acid.[134]

The cause of terpenes activity

Terpenes inhibit fungi due to their lipophilic nature and diverse chemical structures, which allow them to penetrate and disrupt fungal CMs. Their interaction with ergosterol, a key component of mycotic membranes, increases permeability and causes cell leakage. Whereas terpenoid phenols' hydrophobic nature guarantees their preferred partitioning into the lipid membrane or may cause depolarization of membranes.[135] Terpenes also inhibit fungal enzymes, such as chitin synthase and 1, 3-beta-glucan synthases, essential for CW synthesis, compromising structural integrity.[136] Additionally, some terpenes generate ROS, damaging fungal DNA, lipids, and proteins.[137] The oxidation of hydroxyl groups into aldehyde in linear sesquiterpenes reduces their ability to inhibit moulds.[134]

Saponins

Saponins belong to a subclass of terpenoids (glycosides of triterpenes) and sterols, which represent the largest group of PACs. In a glycoside molecule, the sugar component is referred to as the glycone, while one

or more non-sugar organic molecules constitute the aglycone. The aglycone portion can be either a steroid (in steroid glycosides) or a triterpene (in triterpene glycosides).[138]

Saponins (triterpene avenacins and steroidal avenacosides) are structurally intricate amphiphatic glycosides derived from triterpenoids and steroids, commonly formed by natural products, including plants and some marine organisms like starfish and sea cucumbers. The name "saponin" originates from the Latin word *sapo*, meaning soap, due to their surfactant properties, which allow them to form stable, soap-like foam when shaken in water. Chemically, saponins are characterized as high in molecular weight (HMW) glycosides composed of a sugar (glycan) portion attached to a non-sugar (aglycon) component.[139]

Saponins, two types of triterpenes avenacins and steroidal avenacosides, are continuously produced and found in plant leaves and roots. Subgroup Avenacins exist in an active glycosylated form and assemble in the epidermal root cells of tips. They exhibit strong antifungal activity.[139,140]

Saponins extracted from plants like *Glycyrrhiza glabra* (licorice) and *Panax ginseng* (ginseng) interact with ergosterol, creating pores in the fungal plasma membrane. This interaction disrupts membrane integrity, contributing to their antifungal activity.[141]

The antifungal activity MOA of saponins is not completely unknown.[142] The avenacosides active form damages the fungal membrane by creating pores, leading to altered permeability and, consequently, mycotic cell death. The saponin activity is linked to the complex formed between saponin compound interaction with ergosterol, the primary sterol found in fungal membranes.[139,143]

Unlike avenacins, steroidal avenacosides are preserved in plant vacuoles as inactive bidesmosidic form. Steroidal avenacosides become active when plant-infecting fungi injure phytic tissues and interrupt membranes, enabling the phytic ß-glucosidase enzyme to hydrolyze the D-glucose unit. This process converts them into toxic monodesmosides.[139,144,145] The activity of *M. luteus* was inhibited more effectively by sapindoside (SAB) than sapindoside A or B alone. It attacked the lipid content of the CM, causing changing fluidity, permeability, and integrity of the mycotic membrane, eventually causing leakage of the cell contents and, ultimately, cell death.[146] Flowers of *Camellia sinensis* yielded two recently discovered triterpenoid types of saponins, camsinsaponins A and B (1, 2), as well as two recognised congeners (3, 4). These were evaluated for their antimycotic bioactivity against yeasts, including *Candida glabrata, C. albicans,* and *C. tropicalis*. Compounds (1–4) demonstrated outstanding inhibitory effects. Additionally, compounds 1-4 had stronger inhibitory effects on *Candida glabrata* than fluconazole. These findings offer significant insights for the future creation of innovative treatment approaches to combat illnesses that are resistant to drugs.[147]

The cause of saponins activity

Like terpenes, saponins mostly act by permeabilising cellular membranes due to their amphipathic characteristics and disrupting the functions of cells, including organelle integrity, enzyme actions, and other transduction procedures, as well as through triggering apoptosis.[148,149] Saponins and critical signaling pathway interactions highlight the dual capability of saponins to modulate ferroptosis (a unique way for cells to die), thereby offering fresh perspectives for therapeutic action.[150]

Finally, the MP active antifungal components article aligns and supports sustainable development goals (SDGs) by improving good health and well-being (SDG 3), supporting responsible consumption (SDG 12) and production, improving life on land (SDG 15), fostering industry, innovation, and infrastructure (SDG 9), and encouraging global partnerships for goals (SDG 17).

CONCLUSIONS

MPs have long been a cornerstone of traditional medicine, offering a rich source of biologically active constituents with diverse therapeutic properties. Numerous investigations have documented the inhibition of mycosis by metabolites derived from plants and other natural sources. These compounds belong to many different structural classes, such as terpenes, alkaloids, coumarins, and saponins. Understanding the antifungal mechanisms of PACs was critical to providing a scientific basis for the traditional use of MPs in treating FIs and the development of novel AAs with improved efficacy and reduced toxicity. In addition, exploring the diverse MsOA of PACs offers a potential solution to combat resistant fungal strains. This study has highlighted the multifaceted mechanisms by which PACs exert their antifungal effects, ranging from disruption of fungal CMs and inhibition of enzymes, interference with CW synthesis, mitochondrial dysfunction, inhibition of NAs and PS, inhibition of the electron transport chain, decreasing ATP production, and induction of oxidative stress and other mechanisms that may differ slightly compared with antifungal therapy MsOA. These mechanisms not only validate the historical use of MPs in treating FIs but also provide a scientific foundation for their potential as novel AAs.

MPs, with their vast chemical diversity and unique MsOA, represent a promising avenue for the development of effective and sustainable anti-mycosis therapies. By integrating traditional knowledge with modern scientific approaches, researchers can unlock the full potential of these natural resources, paving the way for the discovery of novel antifungal compounds. The exploration of MPs as medical antifungals not only bridges the

gap between traditional and modern medicine but also offers hope for addressing one of the most pressing challenges in global health. By harnessing the power of nature, we can develop innovative antifungal therapies that are both effective and resilient in the face of evolving fungal pathogens.

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CONFLICT OF INTEREST

Author declared that there is no conflict of interest in this research

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