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Coumarin derivatives as antifungal agents – A review

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Abstract: Coumarins and pyridines are a promising class of naturally occurring bioactive heterocycles with unique physical and chemical properties. Compounds containing the coumarin framework possess a wide range of pharmacological, biological, and physiological activities, which makes them important for application in medicine, the food industry and agriculture. Among all coumarins' properties, it was found that coumarins may prevent fungal growth, depending on substituents linked to the coumarin core. Therefore, many coumarin derivatives have been investigated as potentially powerful agents in preventing and controlling fungal pathogens. This review summarises the latest research on coumarins and their antifungal activity to provide useful information for further developing more efficient coumarin-based fungicides.

Keywords: heterocyclic compounds; pyridine; antifungals; mycotoxins; food contaminants

With the world's population rapidly increasing over the years, ensuring an efficient food production system is of the utmost importance. The main threat to food production and security is the presence of fungal pathogens, especially those classified as mycotoxin producers, that can be associated with serious risks to both humans and animals in the term of causing mutagenic, teratogenic, and carcinogenic effects (Terzi et al. 2014; Degola et al. 2015). Along with production losses, crop destruction caused by microorganisms consequently leads to significant environmental pollution and economic losses. Therefore, appropriate crop protection is crucial in ensuring efficient food production, but it also directly affects human health and environmental protection.

In 1985, the risks of mycotoxins encouraged the United States Food and Drug Administration (USFDA) to prescribe the permitted amount of mycotoxins in food. Other countries have also restricted permitted mycotoxins levels in food and feed to preserve human health (Mahato et al. 2019). Additionally, the Food and Agricultural Organization (FAO) and World Health Organization (WHO) have been putting much effort into mycotoxins determination in agricultural products (Kumar et al. 2017).

While more than 300 types of mycotoxins have been identified, *Fusarium* fungal species (*F. graminearum*, *F. culmorum*, *F. sporotrichioides,* and *F. langsethiae)* are among the most problematic species causing plant diseases related to the accumulation of mycotoxins and reduction in production yield (Degola et al. 2015; Alshannaq and Yu 2017). It is estimated that about 25% of the annual world's production of cereals is contaminated by mycotoxins, causing tremendous losses in world production (Alshannaq and Yu 2017). Among various types of mycotoxins, aflatoxins (AFs) are the most toxic and are known to contaminate various food.

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Aspergillus flavus and *Aspergillus parasiticus*, the predominant AF-producing species, can occur in a wide range of agricultural commodities intended for human and animal nutrition, thus causing many adverse effects (Wacoo et al. 2014; Degola et al. 2015; Zani et al. 2015). Some of the most common adverse health effects caused by consuming mycotoxins are estrogenic, gastrointestinal, vascular, urogenital, renal, and neurological disorders and weakening of the immune system. Furthermore, mycotoxins have exhibited high mutagenic, carcinogenic, and teratogenic effects (Terzi et al. 2014).

The application of fungicides has been the most common strategy for preventing and controlling mycotoxins production. However, the long-term use of fungicides can cause fungicide resistance in plant pathogens (Degola et al. 2015). Therefore, the invention of new compounds with potential antifungal activities has become an important target in crop protection. Many coumarin derivatives are proven to possess significant antifungal activity because plants biosynthesise coumarins as a defence against different infections (Kostova 2005). Therefore, many coumarin derivatives are considered potentially strong antifungal agents against pathogenic fungi, which are strongly structure dependent.

Mycotoxins in cereals

Mycotoxins, low molecular weight compounds, naturally originate from different species of filamentous fungi. Therefore, properly identifying and characterising fungi is of the utmost importance in preventing and protecting against mycotoxins (Fakruddin et al. 2015; Alshannaq and Yu 2017). Several genera are associated with mycotoxin producers in cereals, such as *Aspergillus*, *Penicillium*, and *Fusarium* (Terzi et al. 2014; Degola et al. 2015; Alshannaq and Yu 2017). *Aspergillus* and *Penicillium* species commonly occur in foods and animal feeds during storage. In contrast, *Fusarium* species generate wheat, barley and corn in the field and spread out in the plant (Alshannaq and Yu 2017). The presence of fungi on food commodities is dangerous as they cause many diseases such as aspergillosis, aflatoxicosis, coccidioidomycosis, candidosis, cryptococcosis, mycetomas, histoplasmosis, mucormycosis, and paracoccidioidomycosis (Prusty and Kumar 2019).

The most common cereal mycotoxins are AFs, ochratoxins, deoxynivalenol, zearalenone and fumonisins. AFs, zearalenones and fumonisins are usually present in corn, and ochratoxin A in wheat, whereas deoxynivalenols occur in wheat, barley, and corn (Milani and Maleki 2014). Some agricultural products such as corn, peanuts, pistachio, nuts, copra, and coconut have a high potential to be contaminated by AFs, while others such as wheat, oats, millet, rice, soybeans, beans, and pulses are not commonly susceptible to aflatoxin contamination (Kumar et al. 2017). Spices such as black pepper, cardamom, cinnamon, clove, cumin, coriander, and ginger can also be contaminated by AFs, depending on the storage and production conditions (Mahato et al. 2019). Moreover, mycotoxins may be present in fodder, feed, and feed ingredients that can be contaminated by fungi, which produce a large number of different mycotoxins (Terzi et al. 2014), see Table 1.

During food processing, the most common mycotoxins in cereals and other products are not entirely

Table 1. Mayor mycotoxins in food commodities (Smith et al. 2016; Alshannaq and Yu 2017)

Mycotoxin	Fungal species	Food commodity
Aflatoxins B1, B2, G1, G2	*Aspergillus*: *flavus, parasiticus*, *bombycis*, *nomius*, *ochraceoroseus*, *parvisclerotigenus*, *pseudotamarii*, *rambellii*, *toxicarius*	maise, wheat, rice, peanut, sorghum, pistachio, almond, ground nuts, tree nuts, nuts products and seeds, figs, cottonseed, spices, dried fruits, meat, eggs, milk, dairy products
Aflatoxin M1	metabolite of aflatoxin B1	milk, milk products
Ochratoxin A	*Aspergillus*: *ochraceus*, *carbonarius*, *sclerotiorum*, *niger*, *alliaceus* *Penicillium*: *verrucosum*, *nordicum*	cereals, dried vine fruit, wine, grapes, coffee, cocoa beans, cheese, beer, spices
Fumonisins B1, B2, B3	*Fusarium verticillioides*, *Fusarium proliferatum*	maise, maise products, sorghum, asparagus
Zearalenone	*Fusarium*: *graminearum*, *culmorum*, *crookwellense*, *verticillioides*, *equiseti*, *incarnatum*, *pseudograminearum*, *semitectum*, *sporotrichioides*	cereals, cereal products, maise, wheat, barley cereals, banana
Deoxynivalenol	*Fusarium graminearum*, *Fusarium culmorum*	cereals, cereal products

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removed from the material, posing a serious threat to the finished processed food (Milani and Maleki 2014). Agricultural products may become contaminated in different ways and stages of production (in the field or during harvest, transport, and storage (Juan et al. 2012; Fakruddin et al. 2015; Alshannaq and Yu 2017). AFs and *Fusarium*-toxins are common mycotoxins produced on plants before harvesting, while ochratoxin A mostly occurs after harvesting, during storage and after transportation (Terzi et al. 2014). Improper storage under unsuitable temperatures and high humidity provides a suitable environment for fungi growth and subsequent mycotoxin production and contamination (Alshannaq and Yu 2017).

There are two main routes of human and animal exposure to AFs: through direct consumption of AFs-contaminated products and/or through direct consumption of products derived from animals fed with contaminated feed, such as milk and milk products, eggs, meat, and meat products, where AFs remain after processing operations (Degola et al. 2015; Kumar et al. 2017). It was found that aflatoxin M1 (AFM1) can contaminate milk and milk products and can be found in milk in the same concentration as in raw feeds 12–24 h after the animal consumed feed contaminated with aflatoxin B1 (Alshannaq and Yu 2017).

Various strategies have been developed to prevent or reduce mycotoxin formation during the preharvest, harvest, and post-harvest phases of crop production and storage, depending on the type of mycotoxin and its amount in the food or feed sample (Terzi et al. 2014). Good agricultural practices, such as cultivating aflatoxin-resistant varieties and genetic engineering applications, have been employed to prevent and/or reduce aflatoxin contamination at the preharvest stage (Zani et al. 2015). In addition, harvest conditions and storage of agricultural commodities have an enormous influence on the AFs' appearance in feed and grains (Fakruddin et al. 2015). Factors such as temperature, moisture, soil properties, type and length of storage, and climate changes, can contribute to the fungal growth and aflatoxin production in cereals (Kumar et al. 2017; Mahato et al. 2019). Moreover, different factors during storage can also increase mycotoxin presence, such as fungal strain and spores, insects and microorganisms' presence, water, temperature, and oxygen level, drying rate, atmosphere, chemical preservatives, and hygienic conditions (Terzi et al. 2014). Various food processing procedures may also affect the presence of mycotoxins, such as cleaning, milling, brewing, cooking, baking, frying, roasting, flaking, alkaline cooking, extrusion, and thermal treatments (Milani and Maleki 2014; Terzi et al. 2014). However, it is worth mentioning that all of the mentioned processes affect the reduction of final mycotoxins amounts but do not eliminate them completely.

Aflatoxins

Aflatoxins (AFs) are highly toxic secondary metabolites mainly produced by *A. flavus* and *A. parasiticus* and are known to contaminate a wide variety of food. They can occur in a wide range of agricultural commodities intended for human and animal nutrition (Table 1) and can cause a variety of adverse effects (Wacoo et al. 2014; Degola et al. 2015; Zani et al. 2015). *A. flavus* can lead to different diseases in insects, cereal crops, as well as many human diseases, whereby the most hazardous of which are aspergillosis (Fakruddin et al. 2015). Moreover, aflatoxicosis, the disease caused by the consumption of substances or foods contaminated with aflatoxin, may result in acute illness and even death, usually through liver cirrhosis, nutritional and nutritive and immune disorders depending upon dose exposure (Limaye et al. 2018).

The major AFs, among the identified 20, with the highest toxicity, are B1, B2, G1, and G2 AFs (Fakruddin et al. 2015; Mahato et al. 2019), whereas their toxicity varies (B1 > G1 > B2 > G2) (Kumar et al. 2017). The B-types are produced by *A. flavus,* while the G-types are produced by *A. parasiticus* (Kumar et al. 2017).

AFs have a difuranocumarin chemical structure which consists of the coumarin nucleus linked to the bifuran group and a cyclopentane ring (in the case of B-group AFs) or a lactone ring at the other side (Figure 1) (Wacoo et al. 2014; Kumar et al. 2017). These two groups of AFs could be differentiated according to the fluorescence colour; for example, the B-group AFs show blue fluorescence and the G-group show yellow-green fluorescence under ultraviolet light (Wacoo et al. 2014). The biosynthesis of AFs includes 18 enzymatic steps described by Yabe and Nakajima (2004).

Coumarins as antifungal agents

Coumarins. The name coumarin originates from the French term 'coumarou' for the Tonka bean (*Dipteryx odorata*), from which coumarin was first isolated in 1820 by Vogel (Venugopala et al. 2013; Önder 2020). Coumarins (1,2-benzopyrones or *2H*-1-benzopyran-2-ones) represent an important family of naturally occurring benzopyrone compounds formed from benzene and pyrone ring, and its framework is present in many pesticides and pharmaceuticals (Šarkanj et al. 2013).

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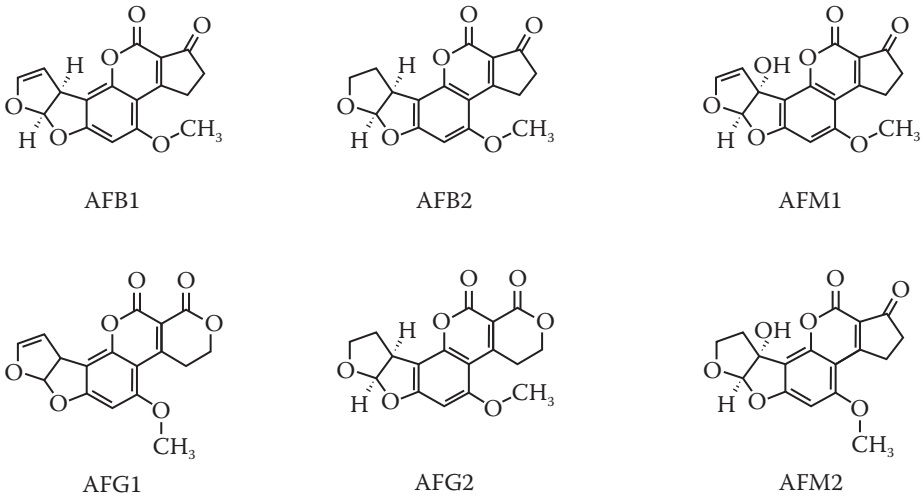

Figure 1. Chemical structures of aflatoxins (Alshannaq and Yu 2017)

They are widely spread in nature and can be found in plant roots (Naseri et al. 2013; Peng et al. 2013; Bai et al. 2016), flowers (Joselin et al. 2012), leaves (Wang et al. 2013; Nguyen et al. 2016; Li et al. 2016; Liang et al. 2020), peels (Dugrand et al. 2013; Ramírez-Pelayo et al. 2019), seeds (Li et al. 2015) and fruits (Li et al. 2019), as secondary metabolites. Coumarins are often found in the plants of *Guttiferae*, *Oleaceae*, *Apiaceae*, *Umbelliferae, Caprifoliaceae*, *Clusiaceae*, *Rutaceae*, and *Nyctaginaceae* families (Prusty and Kumar 2019). They can be present in free form or conjugated with other molecules as glycosides (Yang et al. 2009). Generally, six groups of coumarins are identified, as follows: simple coumarins, furanocoumarins (linear and angular type), pyranocoumarins (linear and angular type), biscoumarins, benzocoumarins and coumestans (Figure 2) (Önder 2020).

The biosynthetic pathway of coumarin synthesis in plants is well described and investigated (Bourgaud et al. 2006; Prusty and Kumar 2019). The biosynthesis of coumarin is mainly related to the higher plants. However, it was also found that several microorganisms, such as fungi and bacteria, may produce coumarin compounds through specific metabolic routes (Costa et al. 2016).

The biological activity of coumarins is associated with their ability to form noncovalent interactions with different active places in living organisms (Ji et al. 2016). Cou-

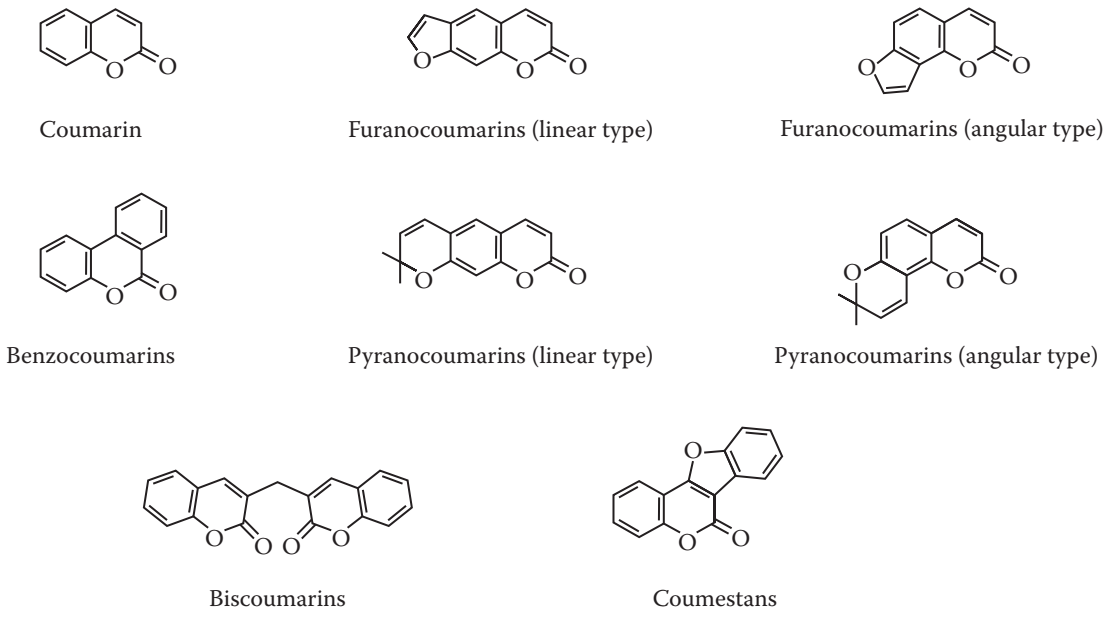

Figure 2. Six basic groups of natural coumarins (Önder 2020)

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Figure 3. Coumarin-thiazolidine-2,4-dione derivatives with antifungal activity (Mangasuli et al. 2018)

marins exhibit a broad spectrum of pharmacological, biological, and physiological activities such as anti-inflammatory (Chen et al. 2017; Liu et al. 2020), antifungal (Renuka and Kumar 2013; Reddy et al. 2014), antimicrobial (Al-Majedy et al. 2017) and antioxidant (Mitra et al. 2013) properties. Moreover, some coumarins show acetylcholinesterase inhibitory activity and thus could be considered a drug in Alzheimer's' disease treatment (Anand et al. 2012; Sandhu et al. 2014).

Furthermore, coumarins are widely used as laser dyes, insecticides, and optical brighteners (Aslam et al. 2010), as well as in perfumes, cosmetics, and additives in food products (Aslam et al. 2010; Ajay Kumar et al. 2015; Prusty and Kumar 2019). In addition, coumarins have an important role in plant biochemistry and physiology, acting as antioxidants, antifungals, enzyme inhibitors and precursors of toxic substances (Šarkanj et al. 2013; Önder 2020). Notably, these compounds are proven to be involved in the actions of plant growth hormones and growth regulators, controlling respiration and photosynthesis (Önder 2020). Seed germination in durum wheat can be inhibited by coumarin, affecting root formation and function, respiration, photosynthesis and nitrogen uptake and metabolism (Chuah et al. 2013).

According to literature data, some coumarin derivatives were proven to prevent fungal growth and possess low cytotoxicity, which is important for their potential application in medicine, the food industry and agriculture (Šarkanj et al. 2013; Prusty and Kumar 2019). It is proven that the antifungal activity of coumarins is strongly structure-dependent (Molnar et al. 2014). It was found that coumarins with a hydroxyl group at position 7 show antibiotic and antifungal properties (Nagamallu et al. 2016). particularly chloro substituents can also contribute to significant antifungal properties of coumarins (Molnar et al. 2014). An additional heterocyclic moiety in the coumarin structure generally contributes to different properties than the starting compound, whereby the resulting compounds often show outstanding properties (Nagamallu et al. 2016).

Antifungal activity of coumarin derivatives. The coumarin framework was found to contribute to enhanced, unique biological properties of coumarin derivatives (Mangasuli et al. 2018). To investigate the antifungal activity of coumarin-thiazolidine-2,4-dione derivatives (Figure 3), two fungal strains (*Candida albicans* and *A. flavus*) were tested (Mangasuli et al. 2018). Methoxy substituent was very important in these derivatives' antifungal activity. Two compounds (1 and 2) with this moiety were the most active compound containing -OCH_3 on both coumarin C_6 and phenyl ring *p*-position (2) was found to be the most active against *A. flavus* and *C. albicans*, while a compound with -OCH_3 at the *p*-position of thiazolidinone phenyl ring and -CH_3 on coumarin C_6 (1) showed good antimicrobial activity. Other compounds showed moderate to good antifungal activity.

Guerra et al. (2015; 2018) showed that coumarin derivatives, 7-hydroxy-6-nitrocoumarin and 4-acetoxycoumarin (Figure 4) are capable of acting as antifungal agents against *Aspergillus* species due to their prevention of the mycelial growth and spore germination, as well as their impact on the structure of the fungal cell wall.

In addition, Khan et al. (2019) synthesised substituted coumarin-3-carboxamide derivatives (Figure 5) and

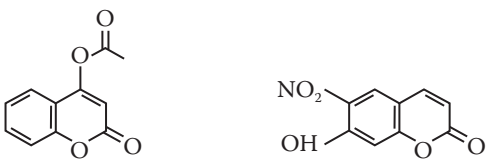

Figure 4. 4-Acetoxycoumarin and 7-hydroxy-6-nitrocoumarin (Guerra et al. 2015; 2018)

Figure 5. Coumarin-3-charboxamide derivatives with antifungal activity (Khan et al. 2019)

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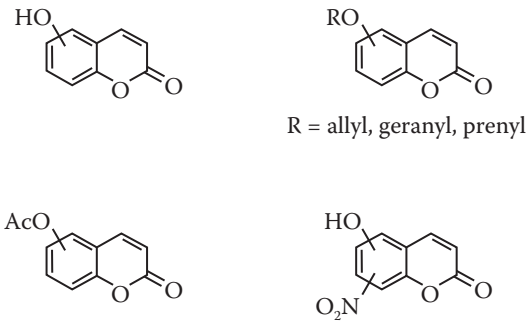


Figure 6. Tested hydroxy-, alkyl-, acetyl- and nitro-coumarin derivatives (De Araújo et al. 2013)

investigated their antifungal activities against various fungal species (*A. niger*, *Aspergillus fumigatus*, *A. flavus*, *Rhizopus*, *Mucor*, *Penicillium*, and *C. albicans*). Among all tested compounds, compounds 3 and 4, with bromo and chloro moiety at the C6 and C8 position of the coumarin ring, showed outstanding activities against *A. fumigatus*, *A. flavus*, and *Rhizopus* species.

De Araújo et al. (2013) investigated the antifungal activities of 24 coumarins, both commercial and synthesised, using *A. fumigatus* and *A. flavus* as tested fungal species. The results indicated that commercial coumarins possess weak or moderate antifungal activity. It was also shown that antifungal activity increased if the electron-withdrawing groups were present in the structure. In addition, it was concluded that *o*-substitution and shorter alkyl chain also contribute to the better antifungal activity (Figure 6).

Further, Kovač et al. (2017) investigated the antifungal and antiaflatoxigenic activities of coumarinyl thiosemicarbazides with substitution in positions 7 and 4 of the coumarin core (Figure 7). *A. flavus* was used as tested fungi. In contrast, the effect of tested compounds was tested at 0.1, 1 and 10 μg·mL^{-1}. The results indicated that substituents in position 7 of the coumarin core contribute positively to the fungicidal activity compared with those in position 4. Compound 5 (*N*-(4-chlorophenyl)-2-(2-((4-methyl-2-oxo-coumarin-7-yl)oxy)acetyl)hydrazine-1-carbothioamide) (Figure 7) showed outstanding properties, inhibiting the aflatoxin production at the

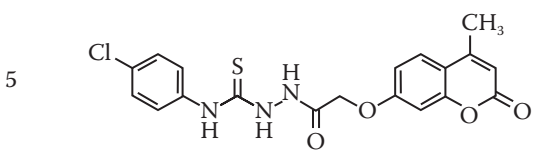


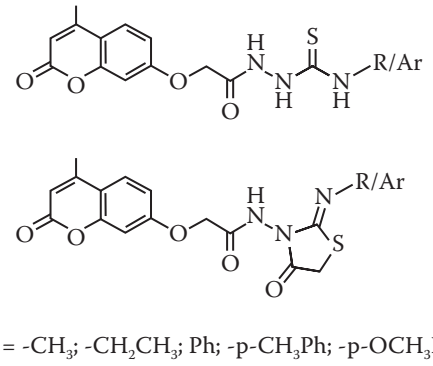
Figure 7. *N*-(4-chlorophenyl)-2-(2-((4-methyl-2-oxo-coumarin-7-yl)oxy)acetyl)hydrazine-1-carbothioamide (Kovač et al. 2017)

concentration of 10 μg·mL^{-1}. Despite the significant antiaflatoxigenic activity, this compound showed moderate antifungal activity, whereas, at a lower concentration of 0.1 and 1 μg·mL^{-1}, it stimulated aflatoxin production. This effect was explained because of the oxidative stress caused by the selected compounds. In addition, it was concluded that aromatic substituents contribute to better antifungal activity than methyl and ethyl substituents.

Šarkanj et al. (2013) obtained several coumarin thiosemicarbazides and 4-thiazolidinones from 7-hydroxy-4-metilcoumarin (Figure 8) as a starting compound and investigated their antifungal activities. *A. flavus*, *A. ochraceus*, *F. graminearum*, and *F. verticillioides* were used as tested fungal strains. The results indicated that all compounds containing a phenyl group in their structure showed excellent antifungal activity against *A. flavus* and were also better than the initial compound, 7-hydroxy-4-methylcoumarin. Both thiosemicarbazide and 4-thiazolidinones with alkyl substituents had the weakest antifungal activity. Additionally, significant antifungal activity against *A. ochraceus* was shown in all compounds containing a phenyl group and one with a methyl group. Moreover, most of the tested compounds showed outstanding antifungal acting on *F. graminearum* species, while *F. verticillioides* was the most stable species among all the tested compounds.

The results concluded that substitution in position 7 with thiosemicarbazide and 4-thiazolidinone moieties contributes to the better antifungal activity of 7-hydroxy-4-methylcoumarin. 4-Thiazolidinones showed better antifungal activity than thiosemicarbazides towards all the tested species, indicating better antifungal activity if substituted phenyl and 4-thiazolidinones rings are included in the structure.

Moreover, Molnar et al. (2014) investigated the antifungal properties of a series of Schiff bases (*E*)-*N*-2-aryliden-



R = -CH_3; -CH_2CH_3; Ph; -p-CH_3Ph; -p-OCH_3Ph

Figure 8. Thiosemicarbazide and 4-thiazolidinone derivatives obtained from 7-hydroxy-4-methyl coumarin as a starting compound (Šarkanj et al. 2013)

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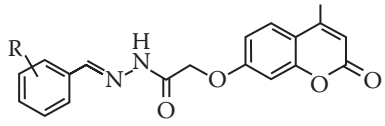

R = -H; -OH; -OCH_3; -OCH_3-OH; -phenoxy; -OH-NO_2; -Cl; -Br; -F; -styryl; -$N(CH_3)_2$

Figure 9. Schiff bases (*E*)-*N*-2-aryliden-2-(4-methyl-2-oxo-coumarin-7-yloxy) acetohydrazide with substituents in position 2, 3, 4 and 5 (Molnar et al. 2014)

2-(4-methyl-2-oxo-coumarin-7-yloxy)acetohydrazide (Figure 9) against four fungal species: *A. flavus*, *A. ochraceus*, *F. graminearum*, and *F. verticillioides*.

The results indicated that compounds bearing the hydroxy group and phenoxy group on the benzene ring showed the best antifungal activity against *A. flavus.* In contrast, those in the halogen group showed weak antifungal activity. Regarding *A. ochraceus* species, the presence of hydroxy and methoxy groups contributed to the enhanced antifungal activity, depending on the position of these groups on a benzene ring. In this case, compounds with methoxy groups showed better antifungal activities than those with a hydroxyl group. Moreover, the antifungal activity of compounds with halogen substituents, those with a hydroxyl group, depended on their position on the benzene ring. Schiff bases with chloro substituents showed the best antifungal activity, while those with fluoro substituent showed no significant antifungal activity. Among all the tested fungi, *F. graminearum* was the most sensitive to the tested coumarinyl Schiff bases, while *F. verticillioides* was the most stable species among all the tested compounds.

In addition, the antifungal activity of substituted phosphoramidate coumarins (Figure 10) was studied by Ji et al. (2016). *C. albicans, A. fumigatus, C. neoformans*, and *A. flavus* were used as tested fungal strains. The results showed moderate to excellent antifungal activity against all the tested fungal species. Compound 6 showed excellent activity against *C. albicans*, greater than fluconazole and polyoxin B. *A. flavus* was extraordinarily inhibited, with compounds 6–9 also showing much better activity than the standard compounds. Generally, compound 6 showed the best activity against all strains and was suggested by the authors as a new antifungal compound.

The inhibition of chitinase plays an important role in developing antifungal agents. Therefore, Batran et al. (2018) studied chitinase inhibitory properties of 4-hydoxycoumarin derivatives containing Schiff base moiety in the coumarin C-3. Additionally, they studied the antifungal activity of these compounds against *Fusarium solani*, *Fusarium oxysporium*, and *A. niger,* as well as pathogenic yeast *C. albicans, Candida tropicalis*, and *Candida krusei*. In contrast, the active antifungal compounds were used for chitinase inhibition activity determination. Compound 10 (Figure 11) showed the best antifungal activity against most tested species and exhibited the highest chitinase inhibition effects.

Renuka and Kumar (2013) studied the antifungal activity of hydrazones and formyl-pyrazoles synthesised from 4-methyl-7-hydroxy coumarin. *C. neoformans*, *A. niger* and *A. flavus*, *C. albicans* were used as tested fungal strains. The results showed that the compounds with *p*-chloro phenyl substituent (11 and 12) (Figure 12) showed outstanding antifungal activities toward all the organisms compared with other tested compounds.

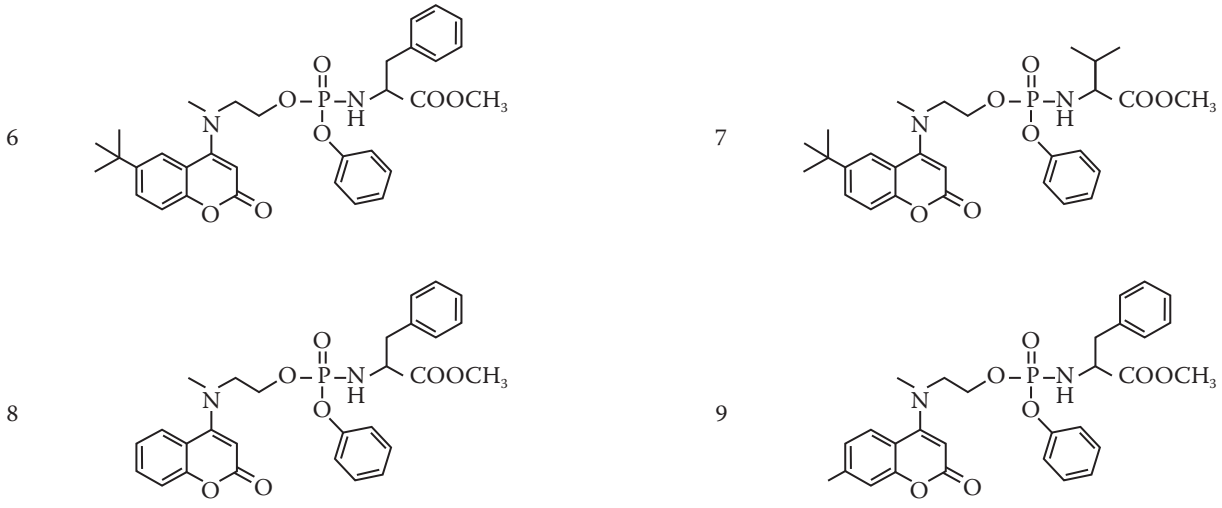

Figure 10. Phosphoramidate coumarins showing antifungal activity against *A. flavus* (Ji et al. 2016)

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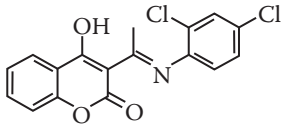
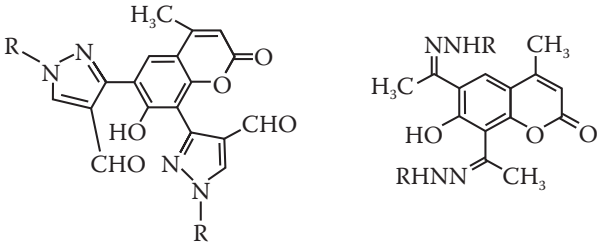


Figure 11. 4-Hydoxycoumarin derivative with antifungal activity (Batran et al. 2018)

Since pyrazole derivatives possess significant biological properties and are mainly used as antimicrobial agents, Nagamallu et al. (2016) investigated the antimicrobial activities of the synthesised coumarin pyrazole derivatives (Figure 13). The dilution technique was used to investigate the antimicrobial activities of pyrazoles linked to the coumarin moiety, such as *bis*-carbazones, *bis*-hydrazones and *bis*-formylpyrazole derivatives. Three fungal strains (*A. niger*, *A. flavus*, and *C. albicanis*) were used to determine antifungal activity, while ciprogloxacin and fluconazole were used as standards. The results showed that all tested compounds exhibited modest antifungal activity (MIC in the range of 12.5 to 100 $\mu g \cdot mL^{-1}$). It was confirmed that compounds with $CONH_2$ and $CSNH_2$ substituents on the carbazone group possess a significant antifungal activity.In contrast, compounds with the $CONH_2$ group in the pyrazole ring showed similar activity as the standard. $CSNH_2$ group on the pyrazole ring showed the highest activity to *A. niger*. In addition, the compound with chloro substituent in the hydrazone group showed moderate antifungal activity, while the same substitution in the pyrazole ring showed weaker antifungal activity. Compounds with methyl substitution showed good activity against *A. flavus* and *C. albicanis*. Compounds with fluoro and methyl substitution, as well as compounds without any substitutions, exhibited the lowest antifungal activity.

In addition, 4-hydroxy-coumarin derivatives were screened for antifungal activity against several fungal strains: *C. albicans*, *Candida glabrata*, *Fusarium oxysporum, A. fumigatus, A. flavus*, *A. niger*, and *Cryptococcus neoformans*. It was found that compound 13, with a 4-hydroxy-3-ethoxy group linked to the phenyl ring, showed the best antifungal activity, while compound 14 also showed a prominent activity against all tested strains (Figure 14) (Tiwari et al. 2017).



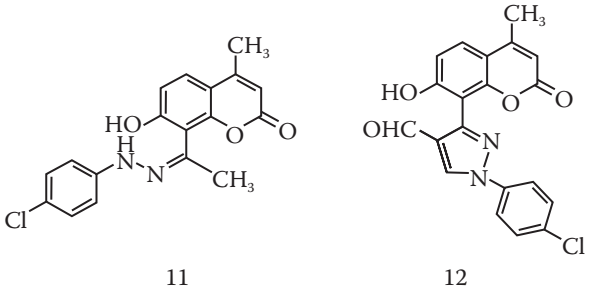
R = C_6H_5; $CH_3C_6H_4$; $OCH_3C_6H_4$; FC_6H_4; ClC_6H_4; $CONH_2$; $CSNH_2$

Figure 13. Pyrazole and hydrazone derivatives investigated by Nagamallu et al. (2016)

Yang et al. (2021) investigated the antifungal activity of coumarins containing the trifluoromethyl group. *Fusarium moniliforme*, *F. graminearum*, and *Curvularia lunata* were used as tested fungal strain. The results indicated that the presence of the trifluoromethyl group enhance the antifungal activity of coumarin thiazoles.

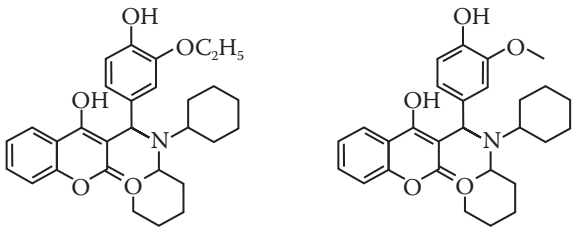
The antifungal and anti-aflatoxicogenic activity of the phytochemical coumarin derivative (5'-hydroxy-aurapten) was tested against *A. flavus* (Ali et al. 2020). It was found that 5'-hydroxy-aurapten has great potential to be used as natural preservatives to protect foodstuffs against *A. flavus* infection.

Moreover, Zhang et al. (2020) investigated the potential antifungal activity of pyrrolecoumarins (Figure 15) against *Rhizoctorzia solani*, *Botrytis cinerea*, *Alternaria solani*, *Gibberella zeae*, *Alternaria leaf spot*, and *Cucumber anthrax.* The research shows that most tested compounds possess certain specific antifungal activity against all the tested fungi, particularly against *R. Solani*. In the case of tested pyrrolecoumarins, it was shown that the presence of alkyl and



11 12

Figure 12. Prominent antifungal agents according to Renuka and Kumar (2013)



13 14

Figure 14. 4-Hydroxy-coumarin derivative (Tiwari et al. 2017)

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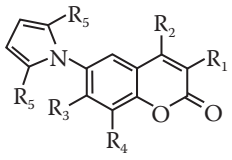

Figure 15. Pyrrolecoumarins (Zhang et al. 2020)

halogen group at the R1 position and methyl group or no substituents at the R5 position decreased antifungal activity, whereas OH group at the R3, methyl group at the R4 and H at the R5 position increase antifungal activity.

A list of the mentioned assays is given in Table 2, providing insight into the assay type and experimental conditions.

Antifungal activity of some coumarin derivatives containing pyridine moiety. Pyridine moiety has also been naturally found in many compounds, and it is well-known that coumarins containing pyridine moiety possess significant anticoagulant, antibacterial and an-

Table 2. Applied methods for coumarin derivatives antifungal activity determination

Genera of fungi	Method	Incubation conditions	Reference
C. albicas and *A. flavus*	disc diffusion method	27 °C, 48 h	Mangasuli et al. 2018
A. fumigatus ATCC 46913, *A. flavus* ATCC 16013)	microdilution broth method	28 °C, 72 h	Guerra et al. 2015
Aspergillus spp. (*A. fumigatus* ATCC 46913 and *A. flavus* ATCC 16013)	microdilution broth method	28 °C, 72 h	Guerra et al. 2018
A. niger, *A. fumigatus*, *A. flavus*, *Rhizopus*, *Mucor*, *Penicillium*, and *C. albicans*	agar well diffusion method	30 °C, overnight	Khan et al. 2019
A. fumigatus strains and *A. flavus* strains	microdilution broth method	25 to 28 °C, 72 h	De Araújo et al. 2013
A. flavus NRRL 3251	dry mycelia weight determination	29°C, 72 h	Kovač et al. 2017
A. flavus (NRRL 3251), *A. ochraceus* (CBS 589.68), *F. graminearum* (CBS 110.250), and *F. verticillioides* (CBS 119.825)	microdilution broth method	35 °C, atmospheric incubator, 48 h	Šarkanj et al. 2013
A. flavus (NRRL 3251), *A. ochraceus* (CBS 589.68), *F. graminearum* (CBS 110.250), and *F. verticillioides* (CBS 119.825)	microdilution broth method	35 °C, atmospheric incubator, 48 h	Molnar et al. 2014
C. albicans CMCC 76615, *A. fumigatus* GIMCC 3.19, *C. neoformans* ATCC 32719, and *A. flavus* ATCC 16870)	two-fold broth dilution method	37 °C, 24 h	Ji et al. 2016
F. solani, *F. oxysporium*, and *A. niger*	agar diffusion technique	28 °C, 72 h	Batran et al. 2018
A. niger, *A. flavus*, and *C. albicanis*	broth dilution method	–	Nagamallu et al. 2016
C. neoformans, *A. niger*, *A. flavus*, *C. albicans*	broth dilution method	–	Renuka and Kumar 2013
C. albicans, *C. glabrata*, *F. oxysporum*, *A. fumigatus*, *A. flavus*, *A. niger*, and *C. neoformans*	standard agar method	25°C, 72 h	Tiwari et al. 2017
Fusarium moniliforme, *F. Graminearum*, *Curvularia lunata*	mycelium growth rate method	27°C, 3–7 days	Yang et al. 2021
A. flavus	isolated from various types of nut products	–	Ali et al. 2020
Rhizoctorzia solani, *Botrytis cinerea*, *Alternaria solani*, *Gibberella zeae*, *Alternaria leaf spot*, and *Cucumber anthrax*	mycelium growth rate method	25°C, 7 days	Zhang et al. 2020

A. – Aspergillus; *C. – Candida*; *F. – Fusarium*

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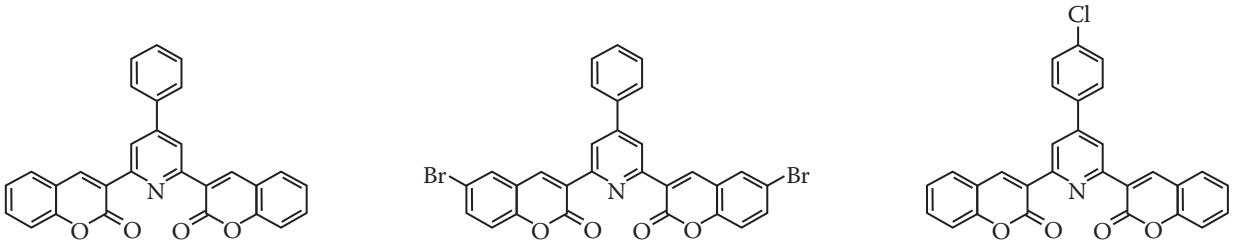
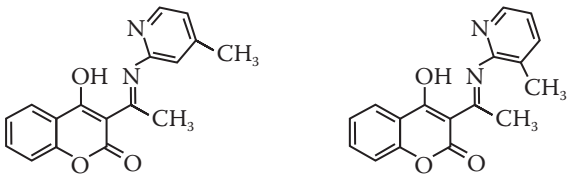


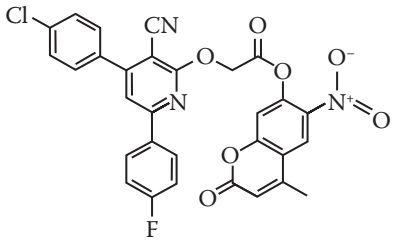
15 16 17

Figure 16. 2,6-bis (1-coumarin-2-yl)-4-(4-substituted phenyl) pyridine derivatives (Kenchappa et al. 2017)



18 19

Figure 17. Antifungal agents, according to Mote et al. (2013)



20

Figure 18. Coumarin pyridin hybrid showing antifungal activity against *C. albicans* (Patel et al. 2020)

tifungal properties (Kenchappa et al. 2017). In order to investigate the antifungal activity of coumarin pyridine hybrids, Kenchappa et al. (2017) used four fungal strains: *A. flavus*, *C. albicanis*, *Microspora geiseous*, and *Aspergillus terreus*. The results showed that the presence of halogen atom, especially bromine, on the coumarin or phenyl contributes to better antifungal activity. Therefore, compounds 15, 16, and 17 were found to possess excellent antifungal activity (Figure 16).

Moreover, Mote et al. (2013) investigated antifungal activities of different Schiff bases of 3-acetyl-4-hydroxy-coumarin and amino pyridines using *A. niger*, *Penicillium chrysogenum*, *Fusarium moneliforme*, and *A. flavus* as tested fungal species. The study showed that all tested compounds possess better antifungal activities towards *Aspergillus* species than other cultures. Compounds 18 and 19 showed the best antifungal activity (Figure 17).

The antifungal potency of coumarin derivatives linked with pyridine moiety was investigated by Patel et al. (2020). This research showed that the chlorine and hydroxy group position on the phenyl ring significantly affects the antifungal potency. It was demonstrated that 4-chlorophenyl substituent (compound 20) increases the antifungal activity against *C. albicans* (Figure 18), whereas other derivatives showed moderate to low activity as antifungal agents. In addition, the *para* position of the hydroxyl group on the phenyl ring decreases antifungal potency.

A list of methods for antifungal activity determination of coumarin derivatives with pyridine moiety is depicted in Table 3, giving insight into the assay type and experimental conditions.

Table 3. Applied methods for coumarin pyridine hybrids antifungal activity determination

Genera of fungi	Method	Incubation conditions	Literature
A. flavus, *C. albicanis*, *M. geiseous*, and *A. terreus*	inoculated on potato dextrose agar media	25 °C, 72 h	Kenchappa et al. 2017
A. niger, *P. chrysogenum*, *F. moneliforme*, and *A. flavus*	poison plate method	room temperature, 48 h	Mote et al. 2013
C. albicans and *A. niger*	soluble dextrose agar	37 °C, 10 days	Darla et al. 2015
C. albicans, A. niger, A. clavatus	broth microdilution method	–	Patel et al. 2020

A. – Aspergillus; *C. – Candida*; *F. – Fusarium*; *M. – Microspora*; *P. – Penicillium*

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CONCLUSION

Fungal pathogens threaten food production and security, especially those classified as mycotoxin producers, which can be associated with serious risks to both humans and animals. Until today, many various strategies have been developed to prevent or reduce mycotoxin formation, whereas the application of fungicides has been the most commonly used method. However, the long-term use of fungicides can cause fungicide resistance in plant pathogens; therefore, the invention of new compounds with potential antifungal activities has become an important target in crop protection.

Many coumarin derivatives are proven to possess significant antifungal activity, both natural and synthetic. It is well established that plants biosynthesise coumarins as a defence against different infections. It was coumarins' antifungal potency varies depending on coumarin core substituents coumarin core, and those with phenolic, hydroxyl, and the carboxylic group have been proven as strong antifungal agents. Halogens as substituents can also contribute to significant antifungal properties of coumarins. In addition, coumarin hybrids with different heterocyclic compounds, such as pyridine moiety, contribute to different properties than the initial material.

Therefore, to prevent negative consequences in food production caused by pathogenic fungi, the development of new compounds with a potential antifungal activity is of significant importance. This review can provide a better insight into the possibility of forming coumarin derivatives as potent antifungal agents.

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