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*Review Article*

# Chemistry and Antifungal Activity of Homoisoflavonoids

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This review deals with the antifungal profile of a subclass of natural products known as homoisoflavonoids. These molecules belong to the larger flavonoids class, yet they are less common for presenting an extra carbon in their basic chemical structures. Homoisoflavonoids are important bioactive molecules because they exhibit promising antimutagenic, antiproliferative, antioxidant, anti-inflammatory, and antimicrobial activity. This review lists the principal experimental studies addressing homoisoflavonoid antifungal activity with the aim of discussing the role of these molecules in obtaining new antifungal agents. The vast majority of research consists of antimicrobial screenings. It was noted that sappanin-type homoisoflavonoids commonly exhibit antifungal activity, but their overall antifungal profile is still very little known. Studies evaluating mechanisms of action are needed to better understand the antifungal potential of homoisoflavonoids.

## 1. Introduction

Homoisoflavonoids are a rare and unusual subclass of natural products that form part of the larger family of flavonoids. They are uniquely characterized by having one more carbon (C-9) in their 16-carbon skeleton than regular flavonoids ($C_6C_3C_6$) (Figure 1). The term homoisoflavonoid was initially used to define the two natural products that were isolated from *Eucomis bicolor* Bak in 1967, eucomin and eucomol (Figure 2). This denomination was considered inadequate, considering that the compounds are not isoflavone derivatives. However, the term homoisoflavonoids came to be widely used to define this group of molecules [1, 2].

The most likely route for the biosynthesis of homoisoflavonoids was proposed by Dewick in 1973 and 1975, in which it was demonstrated that 2′-methoxychalcones are biosynthetic precursors of the homoisoflavonoids. According to Scheme 1, the cyclization of intermediate (II), produced by chalcone (I), would produce either product (III) by the loss of a proton or product (IV) by the addition of a hydride ion. The experiment of Dewick also indicates that eucomin biosynthesis occurs upon the addition of a carbon atom (derived from methionine) to a chalcone-type skeleton with 15 carbon atoms [3, 4].

As of 2019, a total of 295 homoisoflavonoids have been discovered, most of which are found in the plant family Asparagaceae; they can also be found in the Amaryilidaceae, Araliaceae, Fabaceae, Orchidaceae, Polygonaceae, Portolucaceae, Rosaceae, Meliaceae, Polypodeaceae, and Similacaceae [1]. Based on the carbon skeleton, naturally occurring homoisoflavonoids are classified into five groups (Figure 3): sappanin-type (I), scillascillin-type (II), brazilin-type (III), caesalpin-type (IV), and protosappanin-type (V) [3, 5]. The sappanin-type (Figure 3, I) with a basic 3-benzylchromane skeleton is the most common. This subclass encompasses great structural diversity based on C-3 and C-4 substitutions, the location of the double bond on the pyran ring, and the presence (among others) of hydroxyl, methoxyl, methyl substituents, and carbon configurations on the pyran ring [5].

In view of the variety of biological activities attributed to homoisoflavonoids, the compounds have been extensively studied. They are associated with anti-inflammatory activity

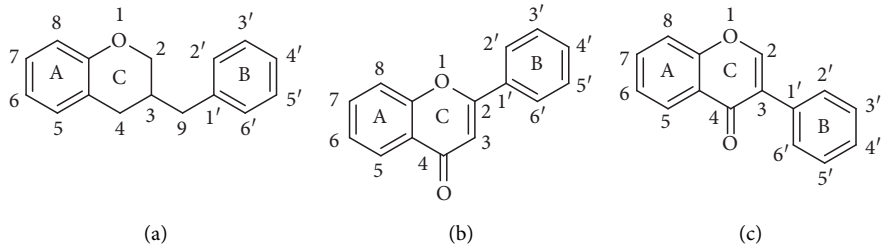



Figure 1: Structural difference between the base skeleton of flavonoids, homoisoflavonoids, and isoflavonoids. (a) Base chemical structure of sappanin-type homoisoflavonoids. (b) Base chemical structure of flavonoids. (c) Base chemical structure of isoflavonoids.

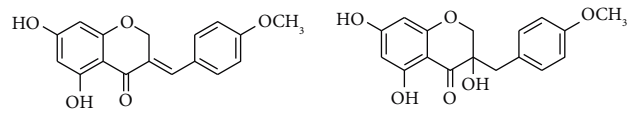
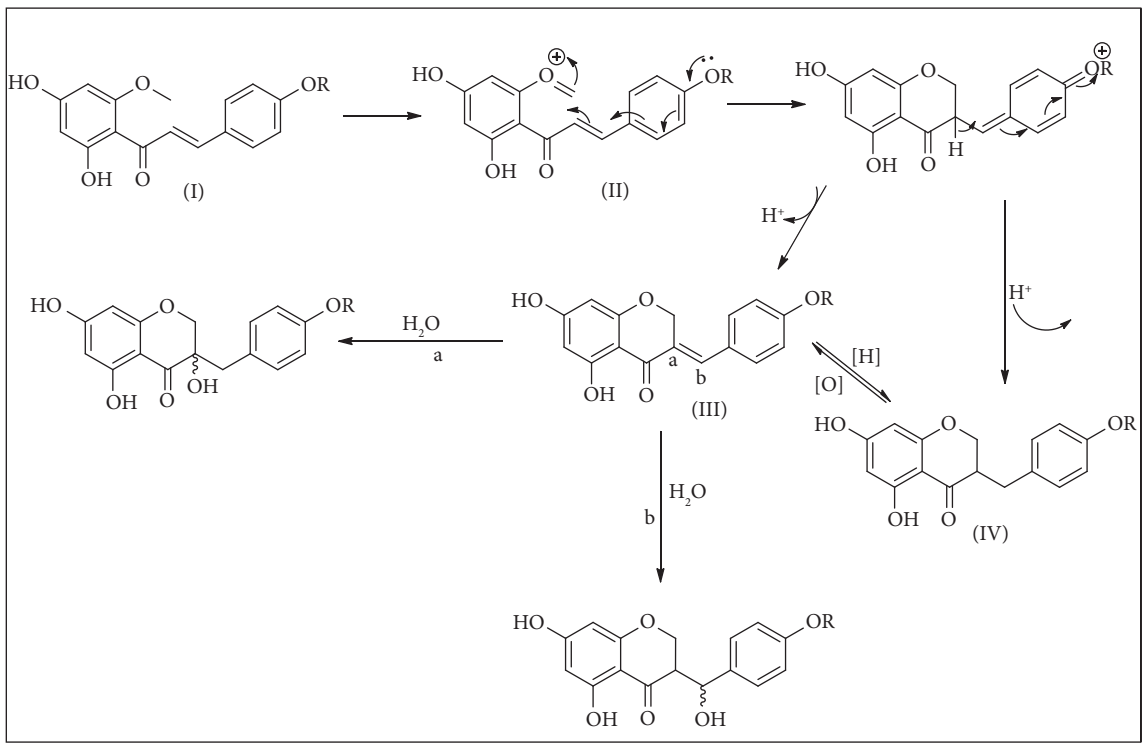



Figure 2: Structures of eucomin and eucomol, the homoisoflavonoids first isolated from *Eucomis bicolor*.




Scheme 1: Possible biosynthetic pathways from 2′-methoxychalcones to 3-benzylchroman-4-one derivatives.

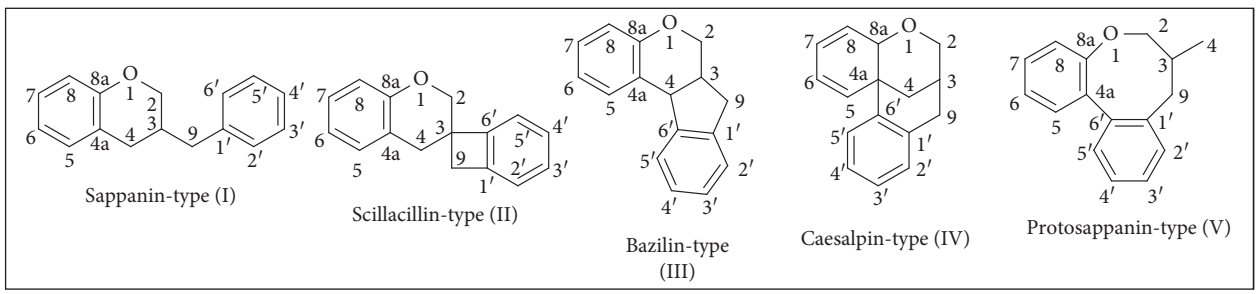



Figure 3: Basic chemical structures of the different types of homoisoflavonoids found in nature.

[6]; cytotoxicity against human cancer cell lines [7, 8]; antidiabetic activity [9]; and antimicrobial activity [10–15]; among others [16, 17].

Each year, fungal infections affect more than a billion people worldwide, with candidiasis representing about 75% to 88% of these infections. Of these, systemic infections are emerging as a major public health problem worldwide. In hospitalized patients, candidemia is the most common form of invasive candidiasis, representing about 9% of all bloodstream infections in the nosocomial environment. Among immunocompromised individuals, the mortality rate from disseminated candidiasis is between 35 and 60%. The *Candida* species most commonly involved in invasive candidiasis are *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* [18–24].

The major problem lies in the fact that multiresistant strains of non-*albicans Candida* (*C. glabrata*, *C. krusei*, and *C. parapsilosis*) are increasingly involved in cases of disseminated candidiasis, making the treatment more difficult and consequently increasing mortality rates. The relatively small number of antifungal agents currently available for therapy, when associated with their indiscriminate use, promotes the development of multidrug-resistant strains, thus leading to the search for new, more potent, and safer antifungal agents [18, 25].

Considering the importance of homoisoflavonoids, this review discusses their antifungal properties and defines (through an evaluation of scientific articles published between 2002 and 2022) their place in the search for new molecules with antifungal profiles.

## 2. Methodology

This literature review was performed using the PubMed and Scopus databases. The search period selected was from January 2002 to August 2022. The following keywords were used: homoisoflavonoids, antifungal activity, antifungal agents, antimicrobial activity, and antimicrobial agents. Scientific articles concerning experimental research published in English were selected. An initial analysis of the title was performed followed by the evaluation of the abstract and using as a selection criterion: performance of antifungal and/or antimicrobial tests with natural or synthetic homoisoflavonoids.

## 3. Results and Discussion

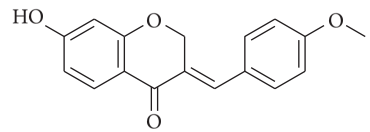
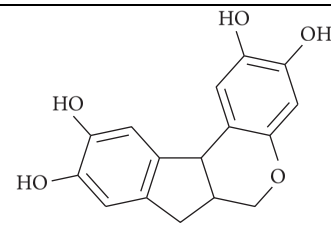
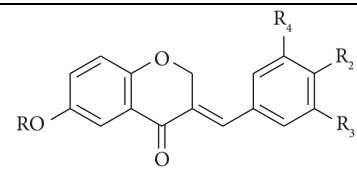
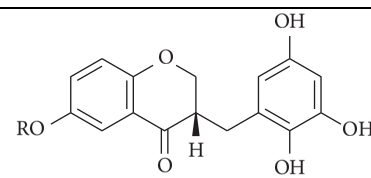
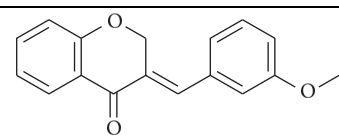
Few studies addressing the antifungal activity of natural or synthetic homoisoflavonoids have been published over the last 20 years (2002–2022). Table 1 summarizes the principal scientific articles selected by this review to discuss the antimicrobial activity and especially the antifungal capacity of homoisoflavonoids. In general, the studies used *in vitro* assays involving microdilutions in broth with a definition of the minimum inhibitory concentration (MIC) or the agar cup bioassay with the delimitation of homoisoflavonoid fungal growth inhibition zones. Species of the genus *Candida*, mainly *C. albicans*, were widely used in the antifungal tests, and considering the increasing number of serious fungal infections involving *Candida* species, these data are indeed relevant. The vast majority of homoisoflavonoids discussed were isolated from differing species of the genus *Caesalpinia*, which in the different regions where they were cultivated enjoyed popular use in treating various health problems, including superficial and mucosal infections.

The study by Reddy et al. is one of the first reports to address the antifungal activity of homoisoflavonoids. The authors evaluated the antifungal capacity of four homoisoflavonoids isolated from *Caesalpinia sappan* L. (Leguminosae) (Figure 4): 4-O-methylsappanol (**1**), protosappanin (**2**), brazilin (**3**), and caesalpin J (**4**), against the *Beauveria* fungus strain *bassiana* ATCC 7159, which grows on silkworms (*Bombyx mori*), using the agar-well method. Compound **1** presented good antifungal activity at a concentration of 100 $\mu$g/mL, as compared to the control (dithane M-45). Both presented a fungal growth inhibition zone of 11 mm. Srinivas et al. extracted and isolated flavonoids from *Ceasalpinia pulcherrima*, such as isobonducellin (**5**) (Figure 4), which in antimicrobial screening using an agar cup test bioassay was evaluated against strains of *C. albicans* (MTCC 3017), *Aspergillus niger* (MTCC 281), and *Rhizopus oryzae* (MTCC 262). Compound **5** (isobonducellin) presented moderate activity against *C. albicans* (MTCC 3017) and *Aspergillus niger* (MTCC 281), with zones of inhibition between 7 mm and 11 mm at respective concentrations of 100 $\mu$g/mL and 150 $\mu$g/mL [11, 29].

In 2008, Rivero-Cruz presented relevant results for the antimicrobial activity of the homoisoflavonoids (Figure 4), hematoxylin (**6**) and brazilin (**3**), against *C. albicans* Ca 54 and various bacterial species involved in human infections. The compounds were isolated from *Haematoxylon brazilian* Karst. (Leguminosae), a large tree, abundant in southeastern Mexico. Tea from the bark of the plant is popularly used to treat stomach discomfort, hypertension, and oral infections, among other conditions. *In vitro* antimicrobial assays were performed for the derivatives using the agar diffusion method, and minimum inhibitory concentrations (MIC) were measured using the broth microdilution method. The antibacterial tests used strains of methicillin-resistant *Staphylococcus aureus*, *Escherichia coli*, and *Enterococci faecium*. The results revealed that the homoisoflavonoids were capable of inhibiting microorganism growth, including *C. albicans* at a threshold concentration of >128 $\mu$g/mL. Compounds **3** and **5** were less potent than the other isolated compounds (gallic acid, methyl gallate, and 4-hydroxycinnamic acid); however, they presented a broad antimicrobial spectrum [10].

Das et al. obtained homoisoflavonoids by extraction and isolation from the aerial parts of *Caesalpinia pulcherrima* (a small leguminous tree found throughout India). The authors prepared homoisoflavonoid derivatives through condensation reactions between 7-hydroxy-4-chromanone or 7-methoxy-4-chromanone and differing substituted aldehydes, a process promoted using a piperidine base (Scheme 2). All of the derivatives were evaluated for antimicrobial activity using an agar cup bioassay methodology with measurement of microorganism growth inhibition zones after 48 h. The derivatives presented bioactivity against

Table 1: Antifungal activity of homoisoflavonoids.

| Antifungal test | Microorganism | Homoisoflavonoid | Result | Reference |
|---|---|---|---|---|
| Agar cup bioassay | (a) *C. albicans* (MTCC 3017),<br>(b) *Aspergillus niger* (MTCC 281) |  | (a) Inhibitory zone 8 mm at 100 $\mu$g/mL and 11 mm at 150 $\mu$g/mL<br>(b) Inhibitory zone 7 mm at 100 $\mu$g/mL and 10 mm at 150 $\mu$g/mL | [11] |
| Agar diffusion method | *C. albicans* Ca 54 |  | MIC > 128 $\mu$g/mL | [10] |
| Agar cup bioassay method | *C. albicans*; *A. niger* |  | Inhibitory zone 5–15 cm at 100 $\mu$g/mL or 150 $\mu$g/mL | [26] |
| Progressive double dilution method | *C. albicans* |  <br>15:R=H<br>16:R=$CH_3$ | MIC = 50 $\mu$g/mL | [27] |
| Microdilution method | *C. albicans* (ATCC 90028), *C. albicans* (ATCC 60193), *C. tropicalis* (ATCC 13803), *C. krusei* (ATCC 6258), *C. parapsilosis* (ATCC 22019), and *C. glabrata* (ATCC 90030) |  | MIC = 62.5 $\mu$g/mL against *C. albicans* (ATCC 90028), *C. tropicalis* (ATCC 13803), and *C. krusei* (ATCC 6258) | [28] |

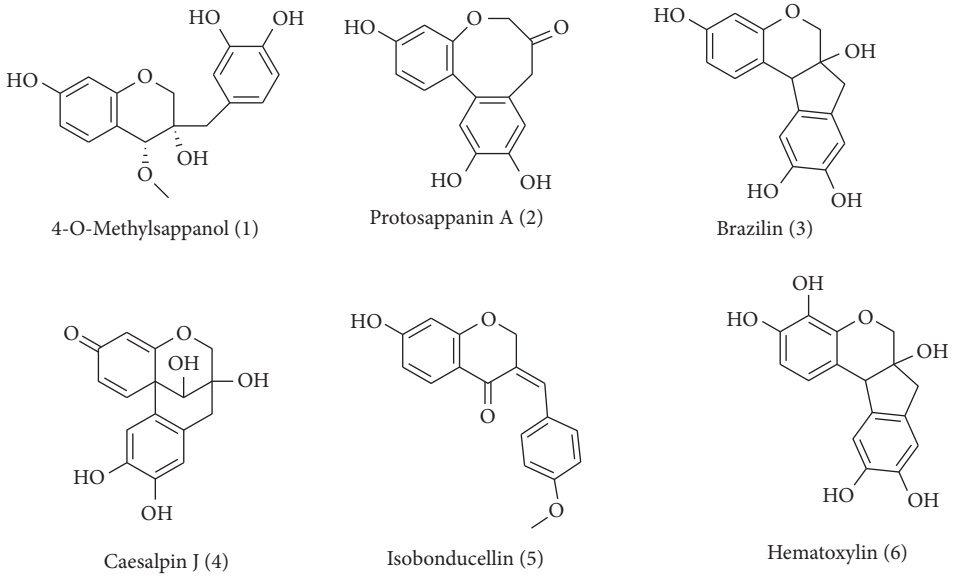
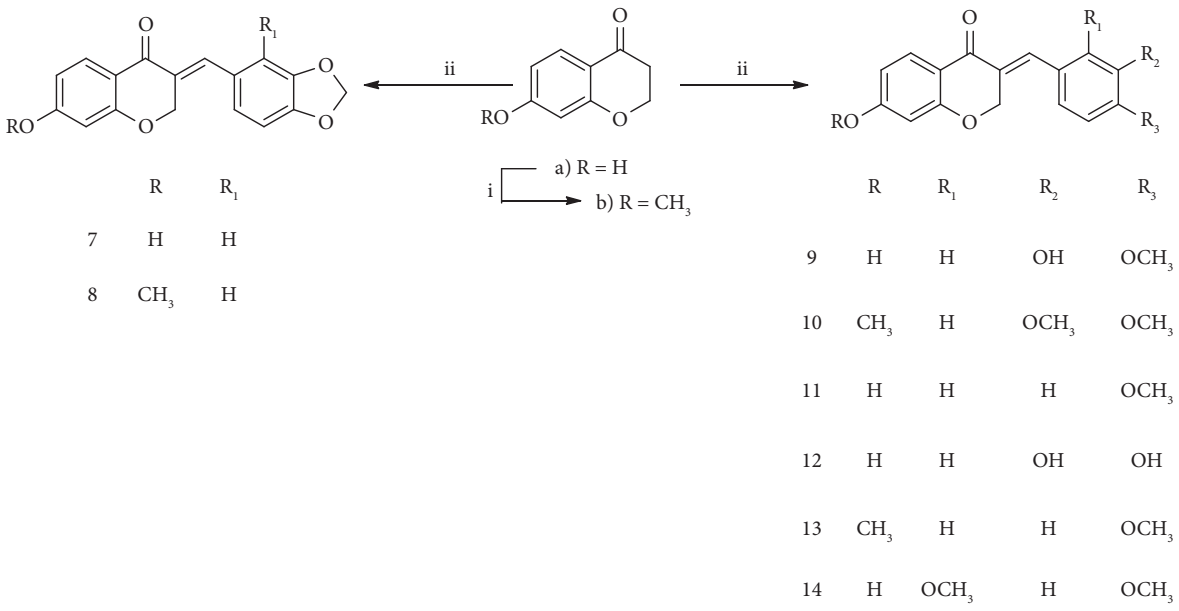



Figure 4: Chemical structures of homoisoflavonoids with antifungal activity.




| | R | $R_1$ |
|---|---|---|
| 7 | H | H |
| 8 | $CH_3$ | H |

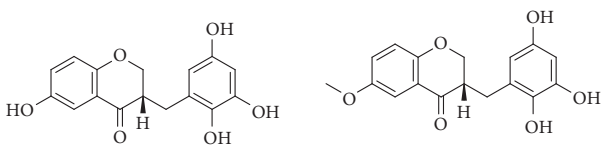
| | R | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|---|
| 9 | H | H | OH | $OCH_3$ |
| 10 | $CH_3$ | H | $OCH_3$ | $OCH_3$ |
| 11 | H | H | H | $OCH_3$ |
| 12 | H | H | OH | OH |
| 13 | $CH_3$ | H | H | $OCH_3$ |
| 14 | H | $OCH_3$ | H | $OCH_3$ |

Scheme 2: Synthetic route used to obtain homoisoflavonoid derivatives of the sappanin-type. Reaction conditions: (i) $CH_3I$, $K_2CO_3$, acetone, 2 h, reflux. (ii) Substituted benzaldehyde, piperidine, 70–80°C, 2 h.

*Aspergillus niger* and *C. albicans* at respective concentrations of 100 $\mu$g/mL and 150 $\mu$g/mL, considering a fungal growth inhibition zone of from 5 to 10 cm. The control used was clotrimazole (inhibition zone 16–20 cm). As to antibacterial activity, the homoisoflavonoids were active against *Bacillus subtilis*, *B. sphaericus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, and *Chromobacterium violaceum* [26].

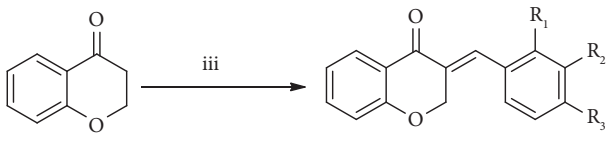
Ata et al. isolated two new homoisoflavonoids from *Caesalpinia bonduc* (Fabaceae) (Figure 5): caesalpinianone (**15**) and 6-O-methylcaesalpinianone (**16**), as well as other previously reported compounds. The molecules were evaluated for their antioxidant and antifungal activity against strains of *C. albicans*. The homoisoflavonoids presented inhibition of fungal growth at a concentration of 50 $\mu$g/mL using a progressive double dilution test method [27].

Famuyiwa et al. evaluated the antimicrobial activity of homoisoflavonoids from the interbulb surfaces of *Scilla nervosa* subsp. *rigidifolia* (an important medicinal plant




Caesalpinianone (15) 6-O-methylcaesalpinianone (16)

Figure 5: Chemical structures of homoisoflavonoids with antifungal activity.




| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 17 | H | H | H |
| 18 | H | H | $OCH_3$ |
| 19 | H | $OCH_3$ | H |
| 20 | $OCH_3$ | H | H |

Scheme 3: Synthetic route used to obtain homoisoflavonoid derivatives of the sappanin-type. Reaction conditions: (iii) substituted benzaldehyde, pyrrolidine, r.t., 24 h.

from southern Africa traditionally used for infection, inflammation, pain/rheumatic fever, and as a laxative, among others). The fungal species used in the study to define the minimum inhibitory concentration was *Saccharomyces cerevisiae*. However, the homoisoflavonoids did not exhibit antifungal activity. Alali et al. also evaluated sappanin-type homoisoflavonoids (isolated from the bulb of *Bellevalia eigii* Feinbrun) against strains of *C. albicans* and *Aspergillus niger* without promising results [30, 31].

The most recent antifungal activity results for homoisoflavonoid derivatives are from an experimental study in our research group, in which Ferreira et al. observed moderate antifungal bioactivity for synthetic homoisoflavonoids (sappanin-type) against *Candida* species. The tested homoisoflavonoids were prepared using an aldol condensation process between 4-chromanone and differing substituted aldehydes, with pyrrolidine as a catalyst, as shown in Scheme 3 [28].

In the microdilution test (CLSI, 2008), derivative **19** presented moderate bioactivity, inhibiting the growth of *C. albicans* (ATCC 90028), *C. tropicalis* (ATCC 13803), and *C. krusei* (ATCC 6258) strains at the concentration of 62.5 $\mu$g/ml. Compound **19** also exhibited fungicidal capacity against these strains at the same concentration. The study suggests that its bioactivity was influenced by the substituent *m*-$OCH_3$ on aromatic ring B [31].

Through *in vitro* tests using the broth microdilution method, Ferreira et al. as mentioned above demonstrated that the antifungal action of homoisoflavonoid **17** does not occur through direct interaction with components of the *C. albicans* fungal plasma membrane or with the cell wall. More advanced studies are needed to clarify the mechanism of action and the relationship between homoisoflavonoid **17′**s chemical structure and its antifungal profile [31].

## 4. Conclusions

In the present review, reports of homoisoflavonoid antifungal activity against various types of fungi were discussed. The small number of reports displays the lack of either phytochemical or synthetic studies involving this chemical class. However, it is important to highlight that in the studies addressed in this review, homoisoflavonoids of the sappanin-type, which are the most common in nature, do exhibit antifungal activity. This indicates that more research studies in this field are needed to better understand which structural characteristics of the basic homoisoflavonoid skeleton are important and/or essential for their antifungal properties and which molecular modifications might be carried out to optimize this bioactivity. Such bioactive compounds can be used as molecular models or prototypes for the design and synthesis of more potent structural analogues. Investigation of mechanisms of action and standardization of experimental protocols is essential to reveal the potential of these compounds as antifungal drug candidates.

## Data Availability

The data supporting this review are from previously reported studies and datasets, which have been cited.

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

## Authors' Contributions

A.R.F. investigated the study and wrote the original draft. D.P.d.S. reviewed the article and supervised the study.

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