



- A Brief Review

RECENT ADVANCES IN CHALCONES AS ANTIINFECTIVE AGENTS

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ABSTRACT

Chalcones are important precursors of flavonoids and isoflavonoids. Naturally occurring and synthetic chalcones show various biological effects, e.g. anti-inflammatory, antitumour, antibacterial, antitubercular, antiviral, antiprotozoal, gastroprotective, and others. Chalcones are lead compounds for the discovery of antioxidant, anti-inflammatory, antitumour and antiinfective agents. This review highlights recent developments of chalcones with antiinfective properties.

Key words: Chalcones, Antiinfective agents, α , β - Unsaturated ketone, 1, 3-Diphenyl-2-propene-1-one

INTRODUCTION

Over the past 25 years, the incidence of systemic fungal infections has been rising dramatically due to an increase in the number of immunocompromised hosts. The search is oriented to find new antifungal drugs, which may selectively attack the fungi without inhibiting any biochemical system of the host.¹⁻³ Chalcones and its derivatives are an object of sustained interest due to their potential activities against herpes simplex virus-1 (HSV-1) and human immunodeficiency virus 1(HIV-1)⁴. This class of compounds also exhibits cytotoxic activity towards leukemia cell lines.⁵

The chalcone class of compounds is known for their anti-infective, especially antifungal and antibacterial activities, since a long time. The word CHALCONE is derived from a Greek word chalcos meaning bronze. Chalcones may exist in two isomeric forms,

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cis- and trans-; the trans isomer is regarded thermodynamically favourable. The chalcone class of compounds has a common structural framework of 1, 3-diphenyl-2-propene-1-one⁶.

Chalcones (Fig. 1) represent an essential group of natural as well as synthetic products and some of them possess wide range of pharmacological activities such as antibacterial⁷, antitumour⁸, anticancer⁹, antitubercular¹⁰, anti-inflammatory¹¹, antioxidant¹², antimalarial¹³, antileishmanial¹⁴, etc. The presence of reactive α , β -unsaturated keto group in chalcones is found to be responsible for their biological activity.

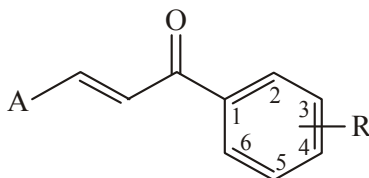


Fig. 1

Natural chalcones have been found mainly as petal pigments, and also occur in the heartwood, bark, leaf, fruit and root of a variety of trees and plants⁶. Chalcone containing plants, such as *Angelica*, *Glycyrrhiza*, *Piper* and *Ruscus* species have been in use as medicine in Asia, Africa and South America¹⁵. Natural chalcones were not isolated until 1910¹⁶. Several pure chalcones were approved for clinical use since then. Some chalcones marketed include metochalcone⁶, a choleric drug and sofalcone⁶, an antiulcer drug. Naturally occurring isoliquiritigenin and isoprenyl chalcone were found to be potent against β -carotene destruction and LDL oxidation¹⁷.

Geranyl chalcone derivatives obtained from the leaves of *Artocarpus nobilis* have antifungal and radical scavenging properties. Derivatives obtained are 2',4',4'-trihydroxy-3'-geranylchalcone (**1**), 2', 4', 4'-trihydroxy-3'-[6-hydroxy-3, 7-dimethyl-2 (E), 7-octadienyl]chalcone (**2**), 2', 4', 4'-trihydroxy-3'-[2-hydroxy-7-methyl-3-methylene-6-octaenyl]chalcone (**3**), 2', 3, 4, 4'-tetrahydroxy-3'-geranylchalcone (**4**), 2', 3, 4, 4'-tetrahydroxy-3'-[6-hydroxy-3, 7-dimethyl-2(E), 7-octadienyl]chalcone (**5**). The chalcones **3** and **5** are new natural products whereas **1** and **2** are reported first time from the family *Moraceae*. All these compounds were found to have good fungicidal activity against *Cladosporium cladosporioides*¹⁸. Five prenylated flavonoids, antifungal chalcones were isolated from *Maclura tinctoria*. Amongst them, isobavachalcone was found to be active against the AIDS-related opportunistic fungal pathogens, *Candida albicans* and *Cryptococcus neoformans* both¹⁹.

Chalcones were first synthesized in the laboratory in the late 1800s²⁰. Chalcones, which are biosynthetic precursors to flavone, are less, than flavones in the plant kingdom. Chalcones with antibacterial properties have been known since the 1940s. Licochalcones showed very potent inhibition against *Bacillus subtilis*, *Staphylococcus aureus* and *Micrococcus luteus*²¹. Lica Pharmaceuticals has introduced a series of amino and diamino containing chalcones with antibacterial properties, generally more potent in inhibition of Gram-positive bacteria²²⁻²⁴.

A series of 2'-hydroxychalcones was found to have antituberculosis activity²⁵⁻²⁶. Chalcones and their heterocyclic analogs are potential therapeutic agents in bacterial diseases. For antibacterial activity, the presence of the enone aggregate (Fig 2) in the molecule is important. Hydrogenated analogues are considered less effective or ineffective, while saturated brominated analogues are effective probably after a metabolic transformation into unsaturated alpha-bromochalcone²⁷.

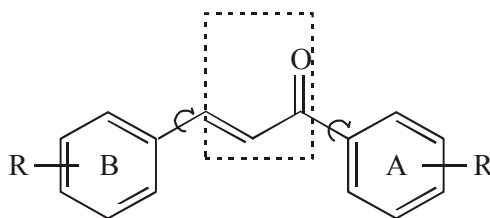


Fig. 2

Chalcones incorporating sulfur, either as part of a heteroaromatic ring (thiophene) or as a side chain (thiomethyl group), showed appreciable activity against a fluconazole-resistant strain²⁸. Chalcones containing piperazine or 2, 5-dichlorothiophene moiety are potentially active against Gram-positive bacteria, *Staphylococcus aureus* and *Escherichia coli*²⁹. Thiazolyl chalcones have been reported to have good antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhosa* and antifungal activity against *Aspergillus niger* and *Candida albicans*³⁰. 2-Pyrazoline derivatives of chalcones are potential antibacterial and antifungal agents.

Some chalcones have other interesting activities like anti-inflammatory properties, anticancer, etc. Since chalcones have been known for a long time, it is difficult to design completely novel and patentable compound within the class. The structurally similar and related flavanoids have also shown good activities³¹.

A biochemical screening to identify the proportions in the clinical use is long overdue. With better understanding of the molecular basis of resistance, it can be envisaged that new diagnostic tools will be developed to allow rapid and appropriate changes in treatment. The use of combinations of fungicides is increasing in medicine and should be a route of choice for overcoming resistance. New chalcone derivatives are under consideration, and in clinical trial, and will be central to therapy in the medium term. The emergence of resistance to these agents can be predicted and it needs advance assessment to provide assistance for their proper integration into drug therapy.

Continued interest in the biological activities of the chalcone class of compounds in both; academia and industry will further define the mechanisms behind the biological activities. Confirmation of specific mechanisms by detailed experimental studies will certainly encourage more drug discovery with this class of compounds.

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