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Review Article

RECENT THERAPEUTIC PROGRESS OF CHALCONE SCAFFOLD BEARING COMPOUNDS AS PROSPECTIVE ANTI-GOUT CANDIDATES

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ABSTRACT

Gout is a common form of arthritis characterized by severe and sudden pain for a long duration, swelling, tenderness, lingering discomfort, and acute redness in the joint situated at the big toe due to the accumulation of monosodium urate (MSU) crystals. Though, at present these drugs have limited pharmacodynamics benefits with the emergence of adverse effects. Therefore, the modern trend has perceived a shift towards the regular use of natural products and tailored-approach, which have revolutionized the prescription pattern from traditional combinations to unexplored classes of drugs. Natural product classes such as chalcones have received adequate attention for treating these severe ailments with a better margin of safety. Chalcone or 1,3-diphenyl-2-propene-1-one or benzylideneacetophenone are the natural scaffold comprising of two aromatic rings connected together by a three-carbon α, β unsaturated carbonyl link. The chalcone scaffold bearing synthetic (polyhydroxylated chalcones, 3,5,2,4-tetrahydroxychalcone, *trans*-chalcone) and natural (sappanchalcone, okanin, hesperidin methylchalcone, quercetin chalcone, 4-hydroxyderricin, isobavachalcone, xanthoangelol F, xanthoangelol, and xanthoangeleol B) compounds have been found to exhibit tremendous anti-gout activity by completely suppressing the active disease proliferating enzyme, xanthine oxidase (XO) as well as by suppressing the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ), along with preventing the formation and influx of pro-inflammatory factors. The overview glance of this scientific review will provide information to the scientists working in the pharmaceutical as well as allied science fields in fabricating, screening, and exploring the abundant hidden chemical classes based on the provided structural, chemical, and miscellaneous aspects.

Keywords: Chalcone, Gout, Inflammation, Xanthine oxidase, NF-κβ, Inhibition

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INTRODUCTION

Gout is a common form of arthritis characterized by severe and sudden pain for a long duration (4 to 12 h), swelling, tenderness, lingering discomfort, and acute redness in the joint situated at the big toe due to the accumulation of monosodium urate (MSU) crystals [1]. It repeatedly produces stern discomfort with burning sensation leading to akinesia in the person suffering from these symptoms, which frequently lasts for weeks [2]. Patients often wake up at late night, thereby, reducing the quality of life. Other affected joints include the fingers, elbows, ankles, wrists, knees, etc. This ailment is continuously rising and in the last two decades, it has affected millions worldwide [3].

Purines are the natural component that exists in the human body and are essentially responsible for the formation of genetic material (DNA). From outside sources such as meat, seafood, strak, etc., the biomolecule is typically procured in its nascent form [4]. The high consumption of alcoholic beverages, tea, and sweetened drinks generally elevates the level of uric acid in the body [5]. However, diet (excessive alcohol intake causes dehydration, decreased metabolism and slow the excretion), obesity, age (symptoms proliferate with increase in age), sex (more in men as compared to women), ethnicity (African-American population is more likely to be susceptible to this condition as compared to the whites), certain medications, medical conditions (abnormal kidney function), family history (increases 20% chances of developing the symptoms in next generation), certain surgery, traumatic situations, low thyroid hormone levels, etc. play a key role in augmenting the level of uric acid [6]. When the kidney fails to eliminate the uric acid due to several reasons, the dissolved high concentration of uric acid in the blood creates MSU under saturated condition. These sharp, needle-like urate crystals deposit in the joint and surrounding tissue that causes severe pain, massive inflammation, and intense swelling in the big toe [7]. The extreme circumstances, these MSU causes recurrent gout, advanced gout (deposit under the skin), and kidney stones (deposition in kidney filtering tubules) [8].

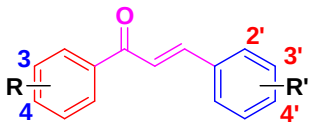
Non-pharmacological way of treatment includes providing adequate fluid intake, absolute control of alcohol, avoiding intake of purine-rich foods and dairy products, weight reduction, etc. Pharmacological treatment involves allopurinol (ALP), lesinurad, febuxostat, and probenecid along with anti-inflammatory drugs like ibuprofen, naproxen, colchicine, and corticosteroids [9]. Though, at present these drugs have limited pharmacodynamics benefits with the emergence of adverse effects. Therefore, the modern trend has perceived a shift towards the regular use of natural products and tailored-approach, which have revolutionized the prescription pattern from traditional combinations to unexplored classes of drugs [10]. Natural product classes such as chalcones have received adequate attention for treating these severe ailments with a better margin of safety.

This review comprehensively highlights (from year January 1951 to December 2018) the reported role(s) of several diversely substituted chalcone scaffold bearing compounds in the management of gout conditions and serum uric acid level by modulating various biological targets along with some patent reports. Various medical, pharmaceutical and research databases were studied by putting the keywords: chalcone, gout, xanthine oxidase (XO), inhibitor, and propene-1-one.

Chalcone

Chalcone or 1,3-diphenyl-2-propene-1-one or benzylidene-acetophenone are the natural scaffold comprising of two aromatic rings connected together by a three-carbon α, β unsaturated carbonyl link (1) [11]. The scaffold received citadel fame owing to different biological effects like anti-diabetic, anti-fibrinogenic, anti-

fungal, anti-gout, anti-histaminic, anti-hyperlipidemic, anti-hypertensive, anti-inflammatory, anti-invasive, anti-leishmanial, anti-malarial, anti-metastatic, anti-microbial, anti-neoplastic, anti-nociceptive, anti-obesity, anti-oxidant, antiplatelet, anti-protozal, anti-retroviral, anti-trypanosomal, anti-tubercular, anti-ulcer, anxiolytic, hypnotic, immunosuppressive, osteogenic, etc [12-17]. Non-pharmacological applications include analytical receptor for Fe(III) determination, artificial sweetener, fluorescent polymers, a fluorescent whitening agent, insecticide, organic brightening agent, polymerization catalyst, scintillator, etc [18-19].



(1)

They are the precursor for flavonoids and isoflavonoid, open chain intermediate in the aurone synthesis, a template for the structure elucidation of chromanochromane, flavanone, flavonoid, and tannins. The flavonoids and chalcones undergo interconversion, wherein the presence of acid, they form chalcone while they form flavonone in the presence of a base [20]. These chromophoric molecules have been first termed as "chalcone" by Kostanecki and Tambor, who synthesized the scaffold in a laboratory from benzaldehyde and acetophenone in the 19th century [21]. The simple pharmacophore for both computational and biological studies and easy steps in the chemical synthesis with a large number of replaceable hydrogens made this scaffold universally popular among the scientific community [22]. At present, chalcone serves as the intermediate template for synthesizing pharmacologically active heterocycle compounds such as pyrazole, pyrimidine, isoxazole, pyrazoline, thiadiazole, benzoxazepine, benzodiazepine, a benzothiazepine, etc. They serve as acceptors in Michael addition reactions [23].

Traditionally, the scaffold is fabricated by employing the Claisen-Schmidt reaction where an equimolar concentration of benzaldehyde and acetophenone are made to react in the presence of 40% base (sodium/potassium hydroxide) solution. In addition to it, numerous name reactions have been reported such as Suzuki-Miyaura reaction, Friedel-Crafts reaction, Julia-Kocienski reaction, Sonogashira isomerization coupling, Carbonylated Heck coupling reaction, Direct crossed-coupling reaction, etc. which ascertain high yield of the product with a larger economic feature. Furthermore, solvent-free reactions, one-pot reactions, microwave-assisted reactions, solid acid catalyst mediated reactions, etc. are also commonly employed modern methods for the fabrication of the benzylideneacetophenone scaffold [24].

Chalcones as anti-gout agents

Synthetic and semi-synthetic chalcones bearing hydroxyl group emerged as potential gout reducing attribute by inhibiting the enzyme actively participating in the proliferation. Polyhydroxylated chalcones have been identified as potential XO inhibitor as suggested by the IC_{50} values in the range of 1.2-290 µM. Compounds (2-3) represented the highest anti-gout activity as indicated by the IC_{50} values of 1.2 µM and 1.3 µM, respectively. The established structure-activity-relationships (SARs) from the molecular docking studies concluded that a minimum of three hydroxyl moieties is crucial for the inhibition of the target enzyme [25].

Investigation of *in vitro* XO inhibitory potential of some multiple hydroxyl group-containing compounds has been reported by Beiler and Martin. The tetra-hydroxylated (4), penta-hydroxylated (5), and methylenedione (6) derivatives exhibited 100% inhibition of the target in the concentration of 0.001 mg/ml [26].

3,5,2,4-tetrahydroxychalcone (7), a non-purine chemical class has been identified as an emerging XO inhibitor by Niu and co-workers as advocated by the IC_{50} value of 22.5 µM. *In vivo* intragastric administration produced a noteworthy decrease in serum uric acid and hepatic XO levels in a dose-dependent manner in hyperuricemic mice model. The kinetic studies through Lineweaver–Burk plot revealed non-competitive inhibition of the target with Ki value of 17.4 µM. The molecule received attention owing to the high level of safety at a dose of 5 g/kg b.w. in acute toxicity studies [27].

Husain *et al.* screened the XO inhibitory perspective of thirty-five molecules synthesized from Claisen-Schmidt reaction. Seventeen compounds have been perceived to express <50% XO inhibitory activity while four molecules presented >50% inhibition of the catalytic enzyme. The inhibitor **(8)** at a concentration of 20 µg/ml displayed the strongest inhibition of XO with an IC_{50} value of 15.31 µg/ml, which was quite comparable with the standard marketed drug ALP (IC_{50} of 12.86 µg/ml) [28].

Analogously, two hydroxylated chalcone compounds (9-10) have been found to drastically inhibit the hepatic XO activity (IC_{50} values 56.8 µM and 47.3 µM) and considerably reduced the serum uric acid level in hyperuricemic mice along with high anti-free radical activity which has a beneficial effect in treating hyperuricemia and gout [29].

Bui and co-workers developed fifteen chalcone derivatives by traditional synthetic route and screened their perspective as an anti-gout agent by inhibiting XO. Five compounds presented notable inhibition of the molecular target with IC_{50} values ranging from 2.4-40.9 µM. Sappanchalcone (11), the natural product from *Caesalpinia sappan*, was a pioneering synthesis by the researcher group, presented an analogous inhibition of XO with that of standard drug ALP (both having an IC_{50} value of 2.5 µM). The caffeoyl-substituted chalcone (12) displayed a better activity than the positive control (IC_{50} of 2.5 µM) [30].

In a similar study, Nguyen *et al.* studied the XO inhibitory potential of sappanchalcone (11) from methnaolic extract of Vietnamese *Caesalpinia sappan*. The natural compounds inhibited the biological target in a concentration-dependent manner with an IC_{50} values of 3.9 µM through competitive manner (Ki of 2.6 µM) [31].

Chalcones obtained from natural sources have been found to exhibit incredible anti-gout activity by inhibition of XO and suppressing the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) activation. Orally administered hesperidin methyl chalcone (13) have been found to considerably reduce the MSU-induced hyperalgesia at 3-30 mg/kg concentration and MSU-induced NF-κβ activation in a dose-dependent manner. The phytoconstituent notably inhibited MSU-induced infiltration of LysM-eGFP+cells (81%), significantly reduces the oxidative stress by downregulating superoxide ion (89%) and nitric oxide radical (48%), prevents synovitis (76%), drastically reduces the NLRP3 inflammasome components mRNA expression by downregulating NLRP3 (72%), ASC (77%), procaspase-1 (71%), and pro-IL-1β (73%) levels. Therefore, the natural product provided relief from the deposition of MSU along with a substantial decrease in the pro-inflammatory components, through inhibition of NF-κβ activation [32].

Quite similarly, the flavonoid precursor trans-chalcone (1) has been found to attenuate the gout symptoms by inhibiting the *in vivo* MSU-induced hyperalgesia, edema, reducing the oxidative stress by downregulating superoxide anion and nitrite radical levels, prevents MSU-induced infiltration of LysM-eGFP+cells and lessening the recruitment of pro-inflammatory cells such as IL-1β, IL-6, TNF-α, and TGF-β at peroral dose of 30 mg/kg dose. The simplest form of chalcone produced both anti-gout and anti-inflammatory effects by inhibiting the NF-κβ activation as well as NLRP3 inflammasome components mRNA expression [33].

Chalcone components isolated from the root bark, stem, leaves, and root cores of *Angelica keiskei* have been screened for their XO inhibitory attribute. 4-Hydroxyderricin (14, IC_{50} = 54.3 µM), isobavachalcone (15, IC_{50} = 27.1 µM), xanthoangelol F (16, IC_{50} = 34.6 µM), xanthoangelol (17, IC_{50} = 8.1 µM), and xanthoangeleol B (18, IC_{50} = 20.3 µM) have been observed to exhibit tremendous anti-gout activity through a mixed-type mechanism [34].

In a phytochemical study, flavanone, aurone, and a chalcone were isolated from the aqueous extract of *Perilla frutescens* leaves. On *in vitro* screening of the phytoconstituents against the prime anti-gout target XO, the chalcone (2',4'-dimethoxy-4,5',6'-trihydroxychalcone) (19) demonstrated the highest inhibition with a micromolar

concentration among them and also showed tremendously high activity as compared to the positive control compound ALP [35].

Few patents related to the chalcone based inhibitors of XO have been reported in the global databases. Throne Research Inc. Ltd. has received a patent in the year 1995 for the development of 2',3,4,4',6'-pentahydroxychalcone (quercetin chalcone, 20) which has immense XO inhibitory characteristics, thereby producing marked anti-gout activity [36].

National Drug Co. Ltd. was credited with a US patent for a chalcone with general formula (21**)** where portion A signifies the substitution of two OH-groups, two OCH_3-groups, and one methylenedioxy group whereas X designates for the substitution of two H-groups, two OH-groups, two OCH_3-groups, and one methylenedioxy group, and at least one of the substituents A and X is two OH-groups [37].

Aventis Inc. Ltd. was awarded a patent in the year 1989 for the development of XO inhibitory active chalcone scaffold comprising of 2,5-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, or 3,4,5-trimethoxyphenyl group in the A-ring and $N(R)_2$ or-NHCOR group in the B-ring [38-39].

Researchers from Taiwan National University were given US patent for the XO inhibitory ability of the phytoconstituent okanin (5). The chalcone compound obtained from the acacia extract expressed impressively high activity with EC_{50} value of 0.074 μM [40-41].

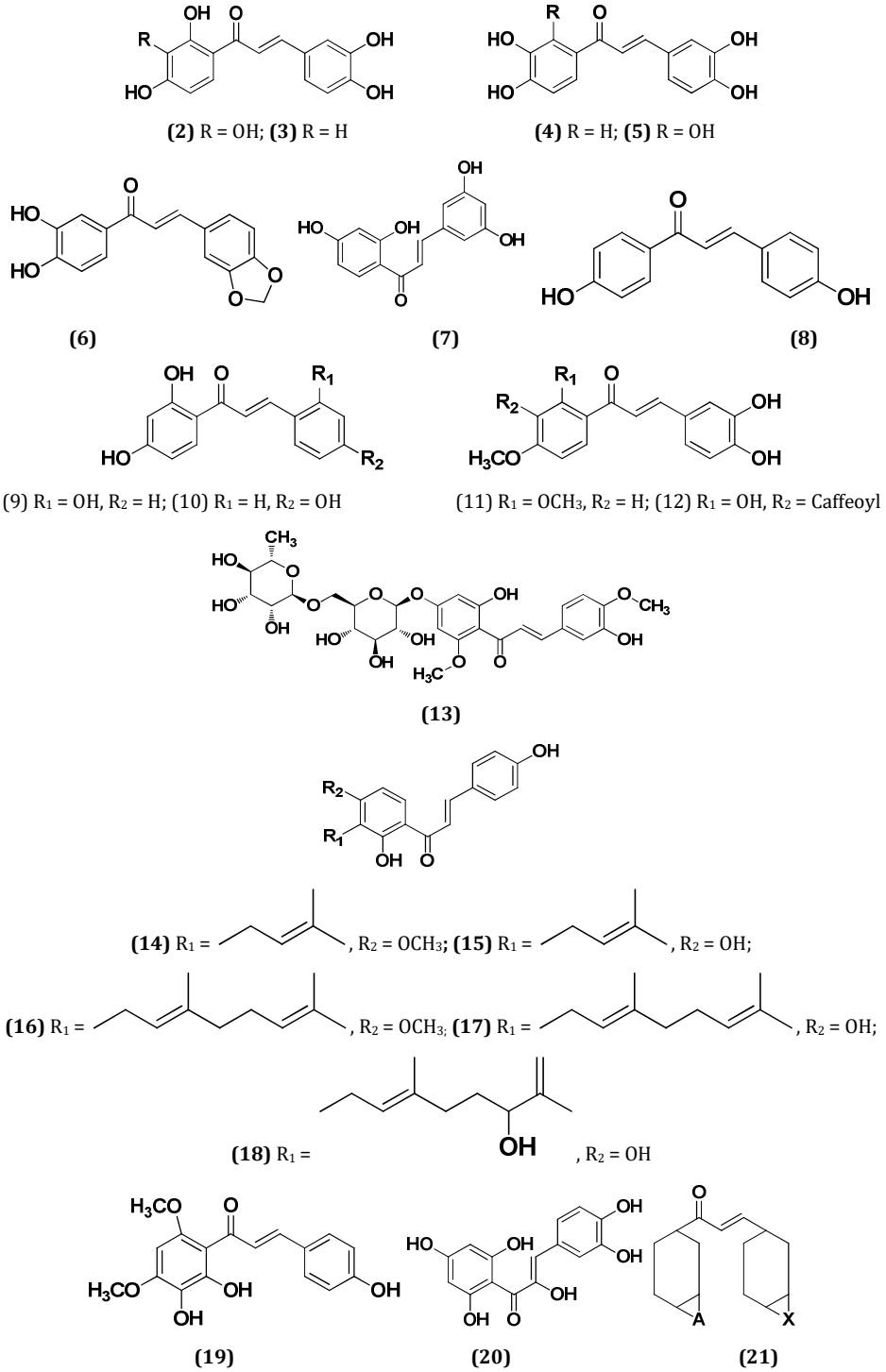


Fig. 1: Chalcone scaffold bearing compounds with prominent anti-gout activity

CONCLUSION

The chalcone scaffold bearing synthetic and natural compounds have been found to exhibit tremendous anti-gout activity by completely suppressing the active disease proliferating enzyme, XO as well as by suppressing the activation of NF-κβ, along with preventing the formation and influx of pro-inflammatory factors. The substituents, particularly the hydroxyl group have played a vital role in inhibiting the biological targets by directly interacting with them by the formation of the hydrogen bonding and various Van der Waals forces, as confirmed by the sophisticated molecular docking and dynamic study tools. Their position and number directly influenced the biological actively considerably. These molecules are at present in their nascent stages which have motivated global researchers towards the further rational development of anti-gout agents having both symptoms reducing capacity in addition to fair anti-inflammatory properties. The overview glance of this scientific review will provide information to the scientists working in the pharmaceutical as well as allied science fields in fabricating, screening, and exploring the abundant hidden chemical classes based on the provided structural, chemical, and miscellaneous aspects.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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