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Pharmacological activities of roburic acid: A review of literature

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Abstract

This review aims to summarize the biological activities of a hopeful phytotherapeutic agent called roburic acid on the basis of literature reports. To date, it has been seen that this triterpene possesses some important biological activities, including anti-infammatory, bone loss inhibitory, and anticancer effects. It is also evident to act against neurological diseases and disorders, gout, bacterial infection, oxidative stress, pox pits, pitting scars, etc. Its anti-inflammatory and anti-prostate cancer effects might be a new hope in the treatment of modern inflammatory and cancer diseases and disorders. Adequate research is necessary on this triterpene.

Keywords: Oak galls, *Gentiana macrophylla*, roburic acid, biological applications

Introduction

Medicinal plants and their devivatives are gaining increasing attention worldwide for their empirical therapeutic efficacy (Zhu *et al*., 2018) [11]. To date, a significant number of plants and their devivatives have been screened and found to have many modern drugs in them. Unfortunately, many medicinal plants and their derivatives remain neglected for years, even decades (Ndjonka *et al*., 2018) [5]. Roburic acid (RA: 3, 4-secoursane type triterpene) (Figure 1) is one of them. A brief description of RA has been shown in Table 1. It was first isolated from the oak galls. However, it was also found in *Gentiana macrophylla* Pall (Wu *et al*., 2012) [9]. Its biological investigation was brought to a halt after the negative results by Verhoff *et al*. (2014) [7], who reported that this triterpene exerted insignificant inhibitory microsomal prostaglandin E2 synthase (mPGES)-1 activity.

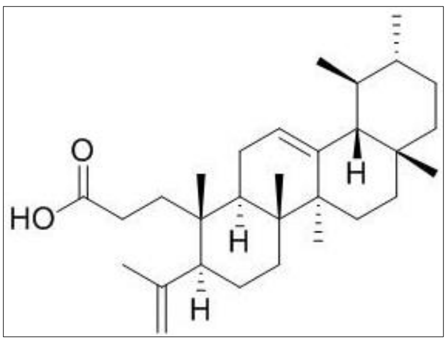

Fig 1: Roburic acid

Table 1: Physical and chemical profile of roburic acid

Chemical group	Tetracyclic triterpenoid, an olefinic compound and a monocarboxylic acid
Synonym	3-[(1S,2S,4aR,4bS,6aR,9R,10S,10aR,12aR)-1,4a,4b,6a,9,10-hexamethyl-2-prop-1-en-2-yl-2,3,4,5,6,7,8,9,10,10a,12,12a-dodecahydrochrysen-1-yl]propanoic acid
Molecular formula	$C_{30}H_{40}O_2$
Biological sources	*Gentiana dahurica* and *Gentiana macrophylla*
Role in plant	Metabolite
Molecular weight	440.7

Although there is a lack of adequate scientific reports on this triterpene, a number of recent studies suggest that this compound might be a good tool in inflammatory and cancer research. This review aims to summarize its impacts on inflammation, bone loss, and cancer on the basis of literature reports in different databases.

Biological activities of roburic acid

Anti-inflammatory effects

Low level inflammation is essential for our body due to it is a type of defensive mechanism. However, chronic and severe inflammation may lead many complex diseases and disorders in our body (Islam *et al*., 2020). In an earlier report (Cao *et al*., 2010) [1], RA was found to inhibit cyclooxygenase (COX)-1 and COX-2 equally. Chen *et al*. (2017) [2] found that RA is able to reduce nitric oxide (NO) and interleukin 6 (IL-6) production. In the former case, it can suppress the expression of inducible nitric oxide synthases (iNOS). In this study, the authors also seen that roburic acid can suppress phosphorylation of inhibitor of κBα (IκBα) and IκB kinase α/β (IKKα/β) along with the translocation of nuclear factor-κB (NF-κB) to the nucleus. Furthermore, it also inhibited the phosphorylation of mitogen-activated protein kinase (MAPKs) including p38 and c-Jun-NH_2-terminal kinase (JNK). Thus, roburic acid might exhibit anti-inflammatory effect on lipopolysaccharide (LPS)-stimulated RAW264.7 macrophage cells through reducing NO and IL-6 production via blocking IKK/IκB/NF-κB and MAPKs pathway, suggesting that it should be a hopeful drug candidate for the treatment of inflammatory diseases.

Neuroprotective effects

The molecular factors underpinning recent failures of β-site amyloid precursor protein-cleaving enzyme-1 (BACE1) inhibitors in Alzheimer's disease (AD) studies have piqued the curiosity of researchers. The elevation of BACE1 by RA raises fresh concerns concerning the development of such β-secretas. When orally dosed inhibitors reach trough levels, a chronic increase may result in uncontrolled BACE1 that boosts substrate processing irregularly. In a study, RA lowered Aβ by dissociating β/γ secretase complexes (Liu *et al*., 2019) [4]. According to this study, RA can be considered as a good candidate in AD as it neither inhibited β- and γ-secretase nor increased BACE1 levels in cell lines and iPSC-derived human neurons.

Effects on bone health

Excessive osteoclast activity may lead to some important skeletal diseases, including osteoporosis and osteolysis (Rachner *et al*., 2011) [6]. RA at 1 to 10 μM was seen to dampen the osteoclast differentiation of bone marrow macrophages (BMMs) without exerting toxic effects on the cells. It did not show any effect on osteoblastogenesis. RA mitigated F-actin ring formation, hydroxyapatite resorption, and gene expression in osteoclasts. It was found to suppress TNF receptor-associated factor 6 (TRAF6), nuclear factor-κB (NF-κB) activity, extracellular regulated protein kinase (ERK) phosphorylation, and calcium oscillations and upregulated the antioxidative response element (ARE) and heme oxygenase (HO)-1 expression. Thus, it suppressed the nuclear factor of activated T cells 1 (NFATc1) activity and the expression of proteins involved in osteoclastogenesis and bone resorption. Additionally, it also acted against bone loss in a mouse model, suggesting that RA can be a good tool in treating osteoporosis and other osteolytic diseases (Wang *et al*., 2022) [8].

Anticancer effects

Although the modern medical science runs a significant paths, but the cancer still remains one of the most fearful diseases in the world. Human cells that have been recruited and converted into pathogenic organisms or tumor building blocks are the agents of destruction in cancer. Cancers both undermine and exploit multicellular organizing systems, and comprehending those raises complex philosophical issues (Hausman, 2019) [3]. RA significantly inhibited tumor necrosis factor (TNF)-induced NF-κB activation in a number of cancer cells. It was found to arrest cell cyle at G0/G1 phase and produce apoptosis in colorectal cancer cells. In this study, RA inhibited the TNF-induced phosphorylation of IKKα/β, IκBα, and p65, degradation of IκBα, nuclear translocation of p65, and NF-κB-target gene expression, including that of XIAP, Mcl-1, and Survivin, in colorectal cancer cells. Additionallt, RA suppressed colorectal cancer cells by blocking NF-κB signaling pathway, suggesting that RA could be a good tool to fight against cancers (Xu *et al*., 2022) [10].

Other biological applications

According to patent reports RA can be used in gout, bacterial infection, oxidative infection, pox pits, pitting scars, and so on (Table 2).

Table 2: Other effects/applications of roburic acid

Preparation/Method	Application(s)	Publication number
Medicinal liquor	Treatment of gout	CN-112546181-A
Feeding additive	Antibacterial anti-oxidant composite nutrient	CN-107996837-A
Preparation method	Qinchuan Tongbi tablet	CN-107569462-B
Roburic acid	Prevention and controls of *Ligusticum wallichii* root rot	CN-107027558-A
Preparation method and application	Prevention and treatment of *Ligusticum wallichii* root rot	CN-107183079-A
Extraction technology	Total alkaloids of radix gentianae macrophyllae	CN-105687308-A
Drug preparation	Treatment of pox pits and pitting scars	CN-105396120-A
Extract	Extraction, related products and uses	EP-3209300-A1
Extract	Extraction, related products and uses	US-2019083561-A1
Extract	Extraction, related products and uses	WO-2016062402-A1
Topical cosmetic or pharmaceuticals	Cosmetics and drug purpose	DE-102014102400-A1
Topical cosmetic or pharmaceuticals	Cosmetics and drug purpose	EP-3110392-A1
Topical cosmetic or pharmaceuticals	Cosmetics and drug purpose	WO-2015128280-A1
Topical cosmetic or pharmaceuticals	Cosmetics and drug purpose	EP-3110392-B1
Promoter	Ceramide production	JP-2014237611-A
Identification method	Certified *Fraxinus bungeana* extract product and its various kinds	CN-103316073-A

Identification method	Certified *Fraxinus bungeana* extract product and its various kinds	CN-103316073-B
Separation and purification method	Roburic acid monomer	CN-102531881-A
Separation and purification method	Roburic acid monomer	CN-102329225-A
Extraction method	Extract preparation and application	CN-102125602-A
Extraction method	Extract preparation and application	CN-102125602-B
Identification method	*Gentiana macrophylla* medicine	CN-101732404-A
Identification method	*Gentiana macrophylla* medicine	CN-101732404-B
Medicaments	Medicinal uses	DE-102009004436-A1

Conclusion

Literature reports suggest that RA might be a good alternative tool to fight against inflammation, neurological diseases and disorders, bone loss, cancers, gout, bacterial infection, oxidative stress, pox pits, pitting scars, etc. Therefore, more research is necessary on this hopeful phytotherapeutic agent.

Conflict of interest: None declared.

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