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REVIEW ARTICLE

The Potential of Xanthones as a Therapeutic Option in Macrophage-Associated Inflammatory Diseases

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ABSTRACT

Xanthones are well known for their significant biological activities and can be found in many herbal medicines. These compounds have the ability to regulate various inflammatory activities and signaling pathways in immune cells, especially macrophages. Macrophages are innate immune cells that can either fuel or dampen an inflammatory response depending on their activation states and play an active role in the development of inflammatory diseases such as atherosclerosis, arthritis, cancer, and diabetes. Many traditional medicines used as a remedy for these diseases contain xanthones, and their bioactivities may be partially attributed to their ability in regulating macrophage responses. In this review, we discuss the *in vitro* and *in vivo* findings on the effects of xanthones on different macrophage immune functions including nitric oxide and cytokine production, migration, polarization, and phagocytosis. Their specific modes of action are highlighted whenever known. We also discuss the potential and challenges in using xanthones as a therapeutic option in various inflammatory diseases. It is hoped that this review can pave the way for future research that focuses on developing xanthones as specific macrophage-targeted therapeutics.

Key words: Anti-inflammatory, inflammation, macrophages, polarization, therapeutics, xanthones

INTRODUCTION

Xanthones are secondary metabolites that can be isolated from many higher plant, fungi, and lichen families. A previous study reported that from 168 species of herbal medicinal plants investigated between 1988 and 2016, 24 families were shown to contain xanthones.[1] They have been reported to be the main constituent of many traditional medicines, such as *Securidaca inappendiculata* Hassk, which is used to treat rheumatoid arthritis[2] and the yellow gum-resin secreted from *Garcinia hanburyi*, which is used to treat infected wound, pain, and edema.[3] Various health supplements containing xanthones are available in the market, and the most common source of xanthones in these products is from either the juice or extract of *Garcinia mangostana* L., which is also known as the mangosteen fruit in Southeast Asia. A few studies investigating the effects of consuming mangosteen products have reported beneficial effects, including having increased antioxidant capacity and reduced levels of C-reactive protein, which is an inflammatory marker.[4-6]

XANTHONE RESEARCH

Each year, discoveries of new xanthones isolated from natural products continue to be reported in journal articles. However, not many of these discoveries have been followed through for drug development, given that there is limited data available on their detailed pharmacological actions, cellular specificity, molecular targets, and bioavailability. Each xanthone molecule has a simple three-ring skeleton. They differ from one another regarding the type and position of substituents present on the core ring, which contribute to their distinct pharmacological properties. A previous study classified xanthones from natural sources into six groups, which are the simple xanthones, xanthone glycosides, prenylated xanthones, xanthonolignoids, bisxanthones, and miscellaneous xanthones, which comprise xanthones with substituents other than the aforementioned ones.[7] Knowledge on xanthone structures has led to the design of a few potential therapeutics that are undergoing clinical trials as cancer treatment, such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA)[8] and gambogic acid.[9] Advances in the field of medicinal chemistry have also enabled structural modifications to be made on xanthones isolated from natural product to create xanthone derivatives with better pharmacological properties such as increased aqueous solubility and cytotoxicity effect against cancer cells.[10]

Majority of the available literature have so far reviewed the role of xanthones as chemopreventive and chemotherapeutic agents.[11,12] This is because xanthones have been shown to exert cytotoxic effects on various cancer cell lines without apparent toxicity on non-cancer cells, potentiating their use as cancer drugs. Other studies have reviewed the antioxidant,[13] antimicrobial,[14] and cardiovascular protective effects of xanthones,[15] but so far, none had specifically reviewed on their ability to modulate immune responses. Many related studies on the effects of xanthones on immune responses have been performed using mice and human macrophage models. Specific macrophage subpopulations have

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