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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been linked to the development of various diseases that are associated with chronic inflammation.[16] In view of this, there is now considerable interest in designing specific therapeutics or compounds that can modulate the functions of macrophages toward desirable clinical outcomes.[17] In this review, we aim to highlight the specific effects of xanthones on various macrophage functions in distinct macrophage models and their underlying mechanisms, based on *in vitro* and *in vivo* studies. Their potential use as immunomodulatory agents that specifically target macrophage functions to alter disease outcomes, and potential challenges, will also be discussed.

MACROPHAGE AND MACROPHAGE-TARGETED THERAPIES

Macrophages are heterogeneous in nature, where each organ has its own specialized resident macrophage population with distinct morphology and function. Depending on the stimuli that they receive from the environment, they can be further activated into either pro-inflammatory (M1) or anti-inflammatory (M2) macrophages. The physiological functions of macrophages include recognizing and killing pathogens, initiating and promoting the resolution of an inflammation, presenting antigens to T-cells, and clearing of host apoptotic cells. Due to their major involvement in chronic inflammation that manifests in various diseases, they have become the main target for new anti-inflammatory therapeutics. Various macrophage-targeting approaches have been designed, such as reducing their production of inflammatory mediators, decreasing macrophage recruitment through disrupting chemokine gradient, and changing their polarization status between M1 and M2.[18] Macrophage-targeted therapy is a relatively new field of research and a few limitations to currently available therapies have been identified, including the development of resistance to the drugs and high cost. Thus, it is important to find new sources of therapeutics, such as bioactive compounds from natural sources, which can potentially be developed into macrophage-targeted therapies in the future.

MOLECULAR EFFECTS OF XANTHONES ON MACROPHAGE FUNCTIONS

Nitric oxide production

Nitric oxide (NO) is produced by many cell types including endothelial cells and macrophages. Pro-inflammatory stimuli such as cytokines and lipopolysaccharide can significantly enhance the production of this enzyme, thus NO levels are usually upregulated during infection and inflammation. Excessive and sustained NO production has been associated with the development of Alzheimer's disease,[19] inflammatory bowel disease,[20] neurodegeneration,[21] and enhanced tumor growth.[22] Many xanthones and their derivatives were shown to have low-to-intermediate effects in the inhibition of NO production by in different macrophage models, including human J774 macrophages, RAW264.7 murine macrophages, and BV2 human microglia cells (brain macrophages).[23-27] These compounds include dulcisxanthone B, 5,9-dihydroxy-8-methoxy-2,2-dimethyl-7-(3-methyl-but-2-enyl)-2H, 6H-pyrano-[3,2b]-xanthone, α-mangostin, cudratricusxanthone A, and 1,3,6,7-tetrahydroxy-8-prenylxanthone (TPX) that were isolated from *Cratoxylum*, *Garcinia*, and *Cudrania* plant genus [Table 1].

Despite their potential as potent NO inhibitors, only few studies have studied the underlying mechanisms of inhibition in detail, mostly in animal cell models. A few naturally occurring xanthones have been reported to suppress inducible NO synthase (iNOS) production, which is one of the main enzymes involved in NO production by macrophages. Mangiferin, α-mangostin, β-mangostin, garcinoxanthone B, and 1,3,5,7-Tetrahydroxy-8-isoprenylxanthone were shown to specifically inhibit iNOS production in RAW 264.7 macrophages.[27-31] In addition, it was reported that β-mangostin and 1,3,5,7-Tetrahydroxy-8-isoprenylxanthone can reduce prostaglandin E2 (PGE_2) production by macrophages without affecting their viability.[27,30] PGE_2 is an enzyme that can stimulate iNOS activity to promote NO production.

Cytokine production

Macrophages can produce high levels of pro- and anti-inflammatory cytokines through various signaling pathways. Activated kinase proteins in the mitogen-activated protein kinases pathway can trigger a signaling cascade that results in the activation and translocation of nuclear factor-kappa B (NF-κB) into the nucleus to induce the transcription of pro-inflammatory cytokine genes. NF-κB activation is central to the pathogenesis of various chronic diseases, including asthma, rheumatoid arthritis, and atherosclerosis,[32] thus many potential anti-inflammatory compounds were tested for their ability to inhibit its activation.

Many studies have claimed that xanthones are anti-inflammatory because they can decrease pro-inflammatory cytokine production

Table 1: The effects of xanthones on macrophage nitric oxide production

Compound (minimum concentration to exert an effect, if known)	Source	Macrophage model	Summary of findings	Reference
Dulcisxanthone B	*Cratoxylum formosum spp. pruniflorum* (roots)	RAW264.7 murine macrophages	IC_{50}=3.9 μM	Boonnak *et al.*, 2006[23]
5,9-dihydroxy-8-methoxy-2,2-dimethyl-7-(3-methyl-but-2-enyl)-2H,6H-pyrano-[3,2b]-xanthone	*Cratoxylum formosum spp. pruniflorum* (roots)	RAW264.7 murine macrophages	IC_{50}=4.3 μM	Boonnak *et al.*, 2006[23]
α-mangostin from methanol extract (50 μM)	*Garcinia cowa*	RAW264.7 murine macrophages	83.4% inhibition of NO production	Wahyuni *et al.*, 2017[24]
Cudratricusxanthone A (2.5 μM)	*Cudrania tricuspidata* (root barks)	BV2 human microglia cells	Inhibition of NO production comparable to 10 μM butein	Yoon *et al.*, 2016[25]
TPX (5 μM)	*Garcinia mangostana* (pericarps)	RAW264.7 murine macrophages	Inhibition of NO production and iNOS mRNA expression in a dose-dependent manner	Li *et al.*, 2018[26]
1,3,5,7-Tetrahydroxy-8-isoprenylxanthone (12.5 μM)	*Garcinia esculenta* (twigs)	RAW264.7 murine macrophages	Dose-dependent inhibition of LPS- and IFN-induced NO production	Zhang *et al.*, 2015[27]

NO=Nitric oxide, TPX=1,3,6,7-tetrahydroxy-8-prenylxanthone, iNOS=Inducible nitric oxide synthase, LPS=Lipopolysaccharide

by macrophages [Table 2]. However, the underlying mechanisms of action are only known for a few of these compounds. Mangiferin, which is a natural phenolic xanthonoid, is a potent inhibitor of NF-κB. Mangiferin at 10 μg/mL was shown to completely inhibit tumor necrosis factor-alpha (TNF-α)-induced activation of NF-κB in U-937 human macrophages.[37] Pretreatment of U-937 macrophages with α- and γ-mangostin was reported to inhibit lipopolysaccharide-induced phosphorylation of MEK, c-Jun N-terminal kinases, signal-regulated kinases and p38 and attenuated the activation of their downstream targets.[35] The same study reported that γ-mangostin was able to prevent IκB-α degradation, which is the inhibitory subunit of NF-κB that needs to be degraded before NF-κB activation. Mangiferin was also shown to inactivate NLRP3 inflammasome in RAW264.7 cells, which is a complex required for the pro-inflammatory IL-1 β secretion.[38] Excessive IL-1 β production has been associated with the development of neuroinflammation and autoimmune diseases such as rheumatoid arthritis. Another compound, cudratricusxanthone A, was reported to inhibit the phosphorylation of the inhibitory subunit IκB-α in a microglial cell model.[25]

Apart from directly suppressing the production of pro-inflammatory cytokines, xanthones may also exert indirect effects to mediate an anti-inflammatory response. DMXAA can activate interferon regulatory factor 3 signaling pathway in mice peritoneal macrophages, which promote interferon-beta (IFN-β) production.[39] IFN-β has been used to treat multiple sclerosis because of its ability to dampen an immune response.[40] Cudratricusxanthone A can induce the expression of heme oxygenase-1 in RAW264.7 mice macrophages, which led to the suppression of pro-inflammatory cytokine production.[34] An interesting observation from previous literature was that the effects of xanthones on cytokine production by macrophages are dependent on macrophage type. For example, α-mangostin has also been shown to promote instead of suppressing the production of TNF-α by monocyte-derived human macrophages.[33] In addition, DMXAA promoted the secretion of a plethora of cytokines from tumor-associated macrophages, including the pro-inflammatory IFN-γ and TNF-α.[41]

Macrophage migration

Macrophages can migrate in response to chemokines and cytokines to the site of tissue damage. While macrophage migration is crucial to allow the clearance of pathogens and initiation of tissue repair, the recruitment of pathological macrophage subpopulations have also been implicated in the development of diseases such as neuroinflammatory diseases, atherosclerosis, and diabetes. Xanthones can prevent the accumulation of macrophages through several mechanisms [Table 3]. TPX from pericarps of *G. mangostana* was shown to inhibit mRNA expression of monocyte chemoattractant protein-1 (MCP-1), MIP-1α, CXCL10, and CX3CL1 in RAW264.7 macrophages.[26] The aforementioned molecules are chemotactic molecules that can attract lymphocytes, monocytes, and macrophages. TPX and α-mangostin also inhibited migration of macrophages toward adipocyte-conditioned media,[26,36] thus has potential in preventing macrophage accumulation in adipose tissues in obesity and diabetes. α-mangostin and γ-mangostin were reported to inhibit expression of CXCL10 in U937 human macrophage model,[35] while DMXAA was shown to inhibit MCP-1 and CXCL10 expression in mice peritoneal and bone marrow-derived macrophages.[42] A few synthesized xanthones have been shown to inhibit the expression of intercellular adhesion molecule-1 (ICAM-1) on endothelial cells, which is a molecule required for transmigration of immune cells across the endothelium. For example, 1,4-dihydroxyxanthone at 65 μg/mL was shown to inhibit up to 86% of ICAM-1 expression.[43] Decreased

Table 2: The effects of xanthones on macrophage cytokine production

| Compound (minimum concentration to exert an effect, if known)	Source	Macrophage model	Summary of findings	Reference
α-mangostin (10 μM)	*Garcinia mangostana* (pericarp and fruit hull)	THP-1 human macrophages	Decreased IL-8 production	Gutierrez-Orozco *et al.*[33]
α-mangostin (4.5 μM)	*Garcinia mangostana* (pericarp and fruit hull)	Human monocyte-derived macrophages	Increased TNF-α production	Gutierrez-Orozco *et al.*[33]
Cudratricusxanthone A (5μM)	*Cudrania tricuspidata* (root barks)	RAW264.7 murine macrophages	Decreased production of TNF-α and IL-1β	Jeong *et al.*[34]
Cudratricusxanthone A (1.3 μM for TNF-α inhibition, 2.5 μM for IL-1β inhibition and 0.6 μM for IL-12 inhibition)	*Cudrania tricuspidata* (root barks)	BV2 human microglial cells	Decreased mRNA levels of TNF-α, IL-1β and IL-12	Yoon *et al.*[25]
1,3,5,7-Tetrahydroxy-8-isoprenylxanthone (12.5 μM)	*Garcinia esculenta* (twigs)	RAW264.7 murine macrophages	Decreased mRNA levels of TNF-α, IL-12p35, IL-12p40, and IL-6, decreased IL-6 production	Zhang *et al.*[27]
α-mangostin (10 μM) and γ-mangostin (10 μM)	*Garcinia mangostana*	U937 human macrophages	Decreased mRNA levels of TNF-α, IL-6, and IP-10	Bumrungpert *et al.*[35]
TPX (5 μM)	*Garcinia mangostana* (pericarp)	RAW264.7 murine macrophages	Inhibited production of TNF-α and IL-6 in a dose-dependent manner	Li *et al.*[26]
			Decreased mRNA levels of TNF-α, IL-6, and IL-1β at 20 μM	
α-mangostin (25 μM/mL)	Chengdu Biopurify Phytochemicals Ltd., China	RAW264.7 murine macrophages	Decreased mRNA levels of TNF-α, IL-6 and IL-1β, increased mRNA levels of IL-10	Kim *et al.*[36]

TPX=1,3,6,7-tetrahydroxy-8-prenylxanthone, IL=Interleukin

Table 3: The effects of xanthones on macrophage chemokine production and migration

Compound (minimum concentration to exert an effect, if known)	Source	Macrophage model	Summary of findings	Reference
TPX (20 µM)	*Gariciania mangostana* (pericarp)	RAW264.7 murine macrophages	Inhibited mRNA expression of MCP-1, MIP-1α, CXCL10 and CX3CL1 Inhibited transwell migration of RAW264.7 macrophages towards adipocytes	Li *et al.*[26]
α-mangostin (25 µM/mL)	Chengdu Biopurify Phytochemicals Ltd., China	Murine peritoneal macrophages and RAW264.7 murine macrophages	Inhibited transmigration of these macrophages with comparable potency to CCR2 inhibitor	Kim *et al.*[36]
α-mangostin (3 µM) and γ-mangostin (3 µM)	*Garcinia mangostana*	U937 human macrophages	Inhibited mRNA expression of IP-10 (CXCL10) when stimulated with LPS	Bumrungpert *et al.*[35]
DMXAA	Not available	Mouse peritoneal and bone marrow-derived macrophages	Decreased mRNA and protein levels of MCP-1 and IP-10	Yu *et al.*[42]

MCP-1=Monocyte chemoattractant protein-1, DMXAA=5,6-dimethylxanthenone-4-acetic acid, LPS=Lipopolysaccharide, TPX=1,3,6,7-tetrahydroxy-8-prenylxanthone
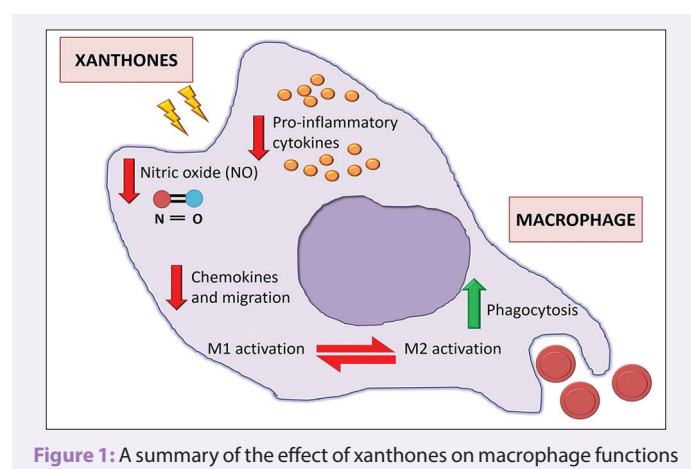
Figure 1: A summary of the effect of xanthones on macrophage functions

ICAM-1 expression may block the transmigration of monocytes, which are the precursors of tissue macrophages, thus reduce the number of macrophages in pathological lesions. The authors proposed that the effect on ICAM-1 expression may be mediated by the hydroxy substitution on the xanthone nucleus, potentially because they can be oxidized to form stable quinonoid.[43]

Macrophage polarization

Macrophages can be polarized into two different activation states, resulting in either M1 or M2 subpopulations. M1 are generally pro-inflammatory in nature and are involved in infection clearance, while M2 are primarily involved in tissue repair. Apart from performing their homeostasis functions, different macrophage subpopulations have been associated with pathology in various diseases.[44] For example, in atherosclerosis, M1 macrophages were reported to contribute to plaque progression, while M2 macrophages participate in plaque regression. Thus, various therapies to decrease macrophage infiltration and to change their polarization status

have been designed, in the hope of altering the course of disease progression.[45]

There are only a few studies which investigated the effects of xanthones on macrophage polarization. A previous study found that treatment of mice with TPX from *G. mangostana* led to polarization of macrophages in adipose tissue toward M2 phenotype.[26] Increased numbers of M1 macrophages in adipose tissue can promote inflammation, leading to insulin resistance in obesity.[46] They reported increased mRNA levels of ARG1 and CD206 and decreased levels of CD11c, which are characteristics of M2 macrophages. Similarly, α-mangostin was also shown to increase CD206 mRNA levels in macrophages from white adipose tissue of obese mice, with a corresponding decrease in CD11c levels.[36] In another study, mangiferin isolated from leaves of *Mangifera indica* Linn. at 100 µmol/L was reported to decrease the expression of M1 macrophage markers CD80 and CD86, in addition to reducing expression of interferon regulatory factor 5, which is a transcription factor that can activate pro-inflammatory genes in macrophages [Figure 1].[47] In contrast, DMXAA, which is an antivascular agent that can prevent tumor development, was reported to polarize macrophage activation status from M2 to M1 phenotype.[48] M2 macrophages are implicated in tumor progression, by promoting growth of tumor and its dissemination. Gambogic acid, which is a xanthonoid, was reported to decrease the expression of IL-6 by RANKL-induced M1 macrophages, which subsequently inhibited their differentiation into osteoclasts.[49] Osteoclasts are involved in bone resorption, leading to the breakdown of bone tissues and causing pathology in diseases such as multiple myeloma.

Macrophage phagocytosis ability

Macrophages are professional phagocytes responsible for eliminating pathogens, tumor cells, and cellular debris. A previous study has reported enhanced phagocytosis of ascitic fibrosarcoma cells by peritoneal macrophages from mangiferin-treated mice.[50] Similarly, in another study, mangiferin was shown to enhance phagocytosis ability of murine peritoneal macrophages when stimulated with various phagocytic targets such as latex beads, red blood cells, and tumor cells.[51] It remains to be

investigated if xanthones can enhance the phagocytosis of pathogenic microorganisms. If proven, hence, xanthones have the potential to be developed into antimicrobial agents that are not only cytotoxic against various pathogens[52,53] but also have the ability to enhance phagocytosis by macrophages to accelerate infection clearance.

In vivo studies

While xanthones have been shown to possess various bioactive properties *in vitro*, it is of greater interest to investigate if these effects can be replicated *in vivo* in various disease settings. In doxorubicin-mediated neuroinflammation model, mangiferin was reported to reduce the brain damage by reducing TNF-α production and oxidative stress.[54] In adjuvant-induced arthritis model, xanthones, particularly 1, 7-dihydroxyl-3-4-dimethoxy-xanthone, showed good potential as antirheumatic agent due to their potent anti-inflammatory effects in downregulating IL-1, TNF-α, and MCP-1 production.[55] α-mangostin and γ-mangostin were able to inhibit tumor growth in experimental colon cancer[56] and mammary cancer.[57] In experimental gastric ulcer, xanthones such as 7-preniljacareubin and 1,3,5,6-tetrahydroxy xanthone were reported to exert anti-ulcer activity through their ability to promote anti-oxidative effects and prevent TNF-α production.[58] However, in experimental ulcerative colitis, it was reported that xanthones may exacerbate the condition, leading to greater colonic inflammation and injury.[59] Further studies are required to understand if any of these effects can be partly attributed to xanthones' role in modulating macrophage functions.

CONCLUSION

Xanthones are a class of compounds with extensive and promising pharmacological properties. Their ability to modulate macrophage functions suggest that they may be useful in treating various diseases where macrophages have been implicated in causing pathology. In addition, xanthones with proven bioactivities such as anti-inflammatory effects may be useful as a therapeutic option in more than one inflammatory disease due to their general effects on macrophage function. However, to fully harness the therapeutic potential of xanthones, there are several areas of future research that require attention. Apart from screening xanthones for their potential bioactivities, studies should also focus on unraveling the exact biological targets of different xanthone compounds and mechanisms underlying these bioactivities. The functional groups on the xanthone skeleton that contribute to their functional activity should be compared and studied in detail. For example, it was proposed that the position of hydroxyl group within the xanthones from *Cudrania tricuspidata* and the presence of a catechol moiety may determine its ability to inhibit NO production.[60] In addition, there is a need to investigate the bioavailability of specific xanthones *in vivo* given their poor aqueous solubility and to find ways to delivery xanthones to target host cells. For example, nanoencapsulation of xanthone and 3-methoxyxanthone in poly (DL-lactide-co-glycolide) significantly enhanced the inhibition of NO production by macrophages, with approximately 74% increase in inhibition.[61] Finally, because macrophages exist in different activation states and there are clear differences between human and mice macrophages, there is a need to carefully select and justify the use of each macrophage model when studying the effects of xanthones on macrophages.

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Conflicts of interest

There are no conflicts of interest.

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