

Recent Updates of the Oral Benefits of Mangosteen Plant Extracts: Review

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Recent Updates of the Oral Benefits of Mangosteen Plant Extracts: Review

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Abstract

Mainly in developing countries, herbal medicine has remained the mainstay of approximately 75 to 80 % of the world population. Mangosteen (*Garcinia mangostana* L.) fruit consists of several active components with major bioactive secondary metabolites that are xanthone derivatives. Traditionally, mangosteen has been used as a remedy for anti-diarrheal, skin infection on account of anti-bacterial, antioxidant, anti-inflammatory benefits which all lead to improving the general health. Nowadays, several studies discuss the benefits of mangosteen, on account of the fact that plenty of recent articles concerning the medical and oral benefits of mangosteen extracts abound. However, still no previous review (up to 2015) covered the oral benefits of the mangosteen.

This review is new in that it addresses the recent updates of the oral benefits of mangosteen extracts. To achieve the study goal, this review covered recent published articles from 2015 onward, which focused only on the oral benefits of mangosteen extracts in use.

The results revealed that oral benefits of mangosteen extracts have been widely used as anti-cancer, anti-inflammatory, and anti-microbes which were evaluated and discussed in this review. To conclude, this review highlighted and addressed the manipulations and oral beneficial effects of mangosteen extracts that were dependent on several active compounds.

It is hoped that this review will be important and beneficial to researchers tackling the future challenges and developments on mangosteen extracts studies.

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Introduction

The number of patients seeking alternate and medicinal plant-based natural products therapy is increasing exponentially. These natural products have been known as potential sources of effective medicinal aids. The subject of such natural sources has a great presence among foundations which take care of good health and conditions. Although they are traditional medicinal products, they are still in use today. In fact, medicinal products and their natural sources maintain a prominent role in health system all over the world. Because of the active ingredients' content derived from plants

and their human body positive effects, most people in the world depend on such medicinal plants. World Health Organization (WHO) has lately recognized the traditional medicine which encompasses the herbal drugs that comprise therapeutic practices which have existed, more often for hundreds of years, before the improvement and spreading of advanced medicine and remain in use till the present time¹. Thus, Mainly in developing countries the herbal medicine has remained the mainstay of approximately 75 to 80 % of the population of the world².

One of the plant-derived medicines is *Garcinia mangostana* Linn which is part of the Guttiferae (syn. Clusiaceae) family and the Latin name for a tropical famous fruit which is commonly known as mangosteen³. It is a plant which grows slowly. It can grow up to 6–25m in height. It roughly produces 4–5 cm flowers that are green or red. It is cultivated mainly in several countries of southeast Asian namely Malaysia,

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Indonesia, Philippines, Thailand, and Sri Lanka^{4,5}. Produced from these countries, mangosteen has also been a major agrarian plant. Its importance is not just taken for its high commercial value but also for its common role as one of the effective herbal plants, which is widely used in different countries of the world such as European countries, Japan, China, the Middle Eastern countries and the United States of America⁶.

Mangosteen, as one of the herbal medicines, is a dark purple or reddish plant from outside. Its pulp is soft, white and juicy edible. Furthermore, from inside it also has a pleasant aroma and a slightly acid flavoured sweet. It is called "The Queen of Fruits" being among the best tasting tropical fruits^{7,8}. In addition, as it assumed to have contents of appealing subjective features for instance, fragrance taste, and visual qualities, richness, nutrient, potential impact and antioxidant strength for lowering the risk of human diseases⁹.

Mangosteen consists of active chemical components, such as xanthenes, phenol, flavonoids, gartanin, saponins, garcinon, tannins, anthocyanins, terpenes, vitamins B1, B2, and other bioactive substances supporting its medicinal properties¹⁰. Xanthenes derivatives are considered major bioactive secondary mangosteen metabolites¹¹. Mangosteen has great efficacy in the whole of its parts, such as seeds, leaves, pulp, and rind due to that consumption of mangosteen has been done frequently for the treatment of several diseases^{12,13}. Traditionally, mangosteen has been used as a remedy for anti-inflammation, antibacterial against gram-negative and positive bacteria, anti-diarrheal, as well as, for skin infection such as eczema¹⁴⁻¹⁷.

Nowadays, there are several studies that discuss the use of mangosteen as anti-cancer, antioxidant, anti-microbial, anti-inflammatory, and anti-hyperglycemic substance on account of having bioactive compounds¹⁷⁻²¹. On account of the fact that there are plenty of recent articles concerning the medical and oral benefits of mangosteen extracts and there has been a previous review that covered the medicinal benefits of the mangosteen plant, this review is new in that it addressed the recent updates of the oral benefits of mangosteen plant extracts.

Materials and methods

Both previous and recent studies focused on the medicinal benefits of mangosteen. A number of studies which prove the benefits of medicinal plants are being conducted in such a field of study. This review titled "Recent Updates of Oral Benefits of Mangosteen Plant Extracts" focused only on the oral benefits of mangosteen and excluded all the topics concerning the other benefits, which mostly were studied on the recent published articles from 2015 onward. Hence, this review aimed to provide the overall recent research updates about the oral benefits of mangosteen plant extracts.

ORAL USES OF MANGOSTEEN

The current review classified the oral benefits of mangosteen plant extracts into many separate areas which included anti-microbes, anti-inflammatory and anti-cancer (Tables 1) that also were evaluated and discussed.

Summary of oral usages of mangosteen extracts

Types of research	Compound extract name	Compound origin	Reference
Oral anti-microbe usages of mangosteen extract			
Anti-cariogenic biofilms	α -Mangostin	Mangosteen peel	[14]
Dental caries prevention	xanthone	Mangosteen pericarp	[22]
Dental caries prevention	α -Mangostin	Mangosteen rind	[29]
Oral bacteria	ethanol	Mangosteen hull	[24]
Oral bacteria	saponin	Mangosteen peel	[25]
Oral bacteria	Ethanol water extract	Mangosteen pericarp	[26]
Dental plaque	Chloroform extract	Mangosteen pericarp	[27]
Oral bacteria	α -Mangostin	Mangosteen pericarp	[20]
Oral bacteria	Flavonoids	Mangosteen pericarp	[23]
Anti-periodontitis bacteria	Gel extract	Mangosteen rind	[12-13]
Anti-oral bacterial	xanthone	Mangosteen pericarp	[28]
Oral anti-inflammatory usages of mangosteen extract			
Gingival inflammation	Whole components	Mangosteen peel	[30]
Dental inflammation	Whole components	Mangosteen peel	[32,34-36]
Dental inflammation	Whole components	Mangosteen rind	[37]
Anti-periodontitis	α -Mangostin	Mangosteen pericarp	[21]
Anti-periodontitis	Gel extract	Mangosteen rind	[12]
Anti-periodontitis	Gel extract	Mangosteen pericarp	[38]
Oral anti-cancer usages of mangosteen extract			
Oral cancer (OSCC)	α -Mangostin	Commercial	[39]
Oral cancer (OSCC)	α -Mangostin	Commercial	[18]
Oral cancer (tongue carcinoma cells)	α -Mangostin	Commercial	[40]

Table 1. summary of oral usages of mangosteen extracts.

ANTI-MICROBES

Streptococcus mutans (*S. mutans*) has been considered as a key etiologic agent which is associated with the initiation of the dental caries, however further organisms can contribute to its pathogenesis. α -Mangostin treated *S. mutans* biofilms at concentrations of 150 mM. This was based on solubility in the vehicle system and bioactivity against planktonic *S. mutans* cells. The studies showed the use of α -Mangostin at 150 mM as effective in reducing the overall biofilm by disrupting the structural integrity and development of *S. mutans* biofilms, suppression of key enzymatic systems connected with the acidogenicity and synthesis of exopolysaccharide¹⁴. Mustaqimah²² showed that the extracts from various parts of mangosteen contain amazing biological properties like anticancer, antimicrobial, antioxidant and which does not contain cytotoxic effects on the fibroblasts of the human gingiva. Furthermore, α -Mangostin derivative from xanthone obtained from the pericarp of mangosteen extract was found to be the most potent anti-microbial activity against cariogenic *S. mutans* on account of affection on the activity of glycolytic enzymes.

Mangosteen pericarp extracts like flavonoids, alkaloids, phenolics, tannins, saponin and triterpenoids that have natural effects inhibit the growth of bacteria, fungi, and viruses. For instance, Hakiki et al.²³ showed that the flavonoids of pericarp extracts of mangosteen with a concentration of 12.5% have antibiogram power on the bacteria *Enterococcus faecalis* (*E. faecalis*) that commonly were discovered after the failure of endodontic treatment. Furthermore, Park et al.²⁴ also showed that the ethanol extract of mangosteen also has bactericidal effects on the *E. faecalis* with 4 μ g/ml as minimum bactericidal concentration value. Likewise, the smear layer of the root canal can be removed by saponin extract of mangosteen peel (0.002%)²⁵. Thus, one of the benefits of mangosteen extract is that it can be used as a root canal cleaner during the time of the management of endodontic treatment failure which was caused by *E. faecalis*. In addition Pribadi, Yonas and Saraswati²⁶ revealed that the mangosteen peel ethanol extract could inhibit the glucosyltransferase enzyme activity from *S. mutans*, that is essential for the progression of dental caries. The common pathogens which cause dental caries

are *S. mutans*, *Streptococcus oralis*, *Streptococcus sanguis*, and *Streptococcus salivarius*. However, Janardhan et al.²⁷ revealed that the crude chloroform of pericarp extract of mangosteen has an effective inhibition zone against that bacteria.

Nittayananta et al.²⁰ showed that there have been effects against oral pathogens such as *Porphyromonas gingivalis* (*P. gingivalis*), *S. mutans*, and *Candida albicans* without cytotoxicity by an oral spray containing α -Mangostin (5 mg/mL) and (250 mg/mL) lawsone methyl ether (2-methoxy-1,4-naphthoquinone). Likewise, 1.59% of xanthone component of mangosteen pericarp extracts showed that it has antibacterial effect on *P. gingivalis*²⁸.

Moreover, mangosteen extract as an adhesive paste that includes α -Mangostin has been applied as an anti-bacterial component that promotes the acid resistance to tooth enamel which leads to preventing dental caries²⁹. Besides, a topical gel of mangosteen rind extracts has been used to cure chronic periodontitis. For instance, the mangosteen rind extracts gel is used to inhibit the growth of *P. gingivalis*, *Actinobacillus actinomycetemcomitans* and also the application of gel extract has the ability to reduce inflammation of gingiva, pocket depth and improve epithelium attachment in chronic periodontitis. Therefore, the gel extract of mangosteen rind in chronic periodontitis cases is perhaps used as adjunctive treatment on scaling and root planning.^{12,13}

ANTI-INFLAMMATORY

Mangosteen and its derivatives not only kill the pathogens in the oral cavity, but also have proven to be effective on dental inflammation. For instance, mangosteen at the concentration of 12.5% have been an anti-inflammatory activity in the rat gingivitis. Thus, the mangosteen extract is perhaps effective for gingival inflammation treatment³⁰.

Moreover, Marzaimi and Aizat³¹ showed that prenylated xanthones such as Mangostin (α , β , γ ,) and gartanin have attracted the interest of most researchers. Several inflammation signalling cascades such as the mitogen-activated protein kinase (MAPK) pathways and nuclear factor kappa-light-chain- enhancer of activated B cells (NF- κ B) have been known to be inhibited by the other forms of prenylated xanthones which are garcinone E and D.

In much the same way, mangosteen peel

extract has the potential in preventing the alveolar bone ridge resorption as well as preserving the tooth extracted socket of by reducing the inflammation. This reduces the receptor activator of nuclear factor- κ B ligand (RANKL) expression and nuclear factor κ B (NF- κ B) that leads to inhibiting the resorption of alveolar bone and accelerating alveolar bone regeneration by increasing the expressions of bone morphogenetic protein-2 (BMP2)³². Likewise, a study proved by Idrus and Kiswanjaya, 2016³³ that the application of *Garcinia mangostana* L. extracts has the potential role in preserving bone loss by decreasing the number of osteoclasts which caused by calvarial bone LPS-infection.

Furthermore, Kresnoadi, Hadisoesanto and Prabowo; Azhar, Kresnoadi and Rahayu; Kresnoadi, Raharjo and Rostiny³⁴⁻³⁶ studies in guinea pigs (*Cavia cobaya*) revealed that the combination of mangosteen peel extract with demineralized freeze-dried bovine bone xenograft (DFDBBX) has the ability to increase collagen 1, osteoblasts, osteocalcin and decrease the expressions of IL-1 β and osteoclasts in the extracted tooth socket. As a consequence, since mangosteen peel extract decreased the PGE-2 and proinflammatory cytokines (TNF- α , IL-1) and inhibited COX-2, moreover osteoclasts formation was inhibited by RANKL either directly or indirectly. As a consequence, there were no occurrence in differentiation and fusion of osteoclast precursors into osteoclasts. Besides, binding of RANKL to RANK receptor on preosteoblasts surface was inhibited, as well. Therefore, the NF- κ B activation was inhibited, and the osteoclasts number were reduced. Therefore, the administration of mangosteen peel with a combination of DFDBBX is the most effective material that can promote the preservation of extraction socket and alveolar bone regeneration.

Dennis et al.³⁷ also reported that in vivo a study of the mangosteen rind extract as an anti-inflammatory effect with concentration 5% and 10%, leads to a reduction of inflammatory cells until wound healing in the rabbit teeth. Meanwhile, mangosteen rind extract of concentration 10% could be used to treat reversible pulpitis.

A recent study revealed the IL-8, IL-6 expression and PGE₂ are inhibited⁶ by mangosteen extract at 1 μ g/ml in 5 μ g/ml P.

gingivalis LPS-treated human gingival fibroblast²¹. Furthermore, Hendiani et al. and Mahendra et al.^{12,13,38} revealed using topical gel of mangosteen rind extracts with scaling and root planning is more effective in reducing pocket depth (PPD) in gingival inflammation, and bleeding compared to the plain scaling and root planning therapy. Thus, the gel of mangosteen rind extract has been an adjunctive therapy in periodontal treatment.

ANTI-CANCER

Xanthone is present in high quantity in mangosteen, as α -Mangostin is proved to exert synergistic impact on human oral squamous cell carcinoma (OSCC) when combined with anticancer drugs. The combination of α -Mangostin with (TNF)-related apoptosis-inducing ligand (TRAIL) induced apoptosis of SAS cells through the mitochondrial pathway through activation of caspase-9 and -3/7, following the cytochrome *c* releasing³⁹. Furthermore, Kwak et al.¹⁸ revealed that the OSCC cell proliferation is inhibited and the cell death is induced by the α -Mangostin through the intrinsic apoptosis pathway and arresting of the cell cycle at the G1 phase in a time and dose-dependent manner with a little to no effect on normal human PDLF cells. Thus, α -Mangostin has been considered as an agent that is potentially effective in the treatment of OSCC.

Other study conducted by Lee et al.⁴⁰ investigated the tumor xenograft mouse model (tongue mucoepidermoid carcinoma cells). α -Mangostin inhibition effects on the treated mice bearing YD-15 tumor xenografts significantly exhibited a reduced weight and volume of tumor on account of the promoting potent effects of α -Mangostin on apoptosis cancer cell. Immunohistochemical analysis showed an increase in the cleaved caspase-3 level, however the levels of Ki-67, p-ERK1/2 and p-p38 reduced in the treated mice with α -Mangostin.

Conclusions

This review covered the recent articles related to the oral benefits of the mangosteen plant extracts. Among the several components of this plant, it was found that xanthenes derivatives have the most contributions. Obviously, the oral benefits included by mangosteen plant extracts were poured into anti-cancer, anti-bacterial, anti-inflammatory and anti-cariogenic. For instance,

those mangosteen components were used to inhibit oral cancers, dental caries biofilms, bacterial growth, and gingival inflammation. Furthermore, it was applied as a root canal cleaner during the management of the endodontic treatment failure. It was also used as adjunctive treatment on scaling and root planing in periodontal cases, as well. In spite of the widespread contributions and benefits that the mangosteen plant extracts encompass, its application is still limited, especially clinically. Thus, in order for it to become a prescription drug, more human research is required to prove its therapeutic effects clinically.

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Declaration of Interest

The authors report no conflict of interest.

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