Journal of Applied Pharmaceutical Science Vol. 10(07), pp 127-146, July, 2020
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2020.10716
ISSN 2231-3354

A review on phytochemical constituents, role on metabolic diseases, and toxicological assessments of underutilized part of *Garcinia mangostana* L. fruit

Abdul Rohman[1*], Fitriana Hayyu Arifah[1], Irnawati[1,2], Gemini Alam[3], Muchtaridi[4], Muhammad Rafi[5]

[1]Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia.
[2]Faculty of Pharmacy, Universitas Halu Oleo Kendari, Southeast Sulawesi 93232, Indonesia.
[3]Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia.
[4]Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy Universitas Padjadjaran, Sumedang, Indonesia.
[5]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Bogor Agricultural University, Kampus IPB Dramaga, Bogor, Indonesia.

ARTICLE INFO

Received on: 20/09/2019
Accepted on: 12/02/2020
Available online: 04/07/2020

Key words:
Garcinia mangostana L., metabolic disease, phytochemistry, toxicological assessment, underutilized part.

ABSTRACT

Metabolic diseases are one of the problems in public health and become the major causes of mortality. These have led the scientist to solve the metabolic disease-related problems by exploring some natural medicine and phytochemicals to prevent and to treat them. One of the plant medicines potential to be developed is *Garcinia mangostana* L. or mangosteen which belongs to the family Clusiaceae. The underutilized part of the fruit including pericarp and seed is a promising candidate as herbal medicine, particularly to treat and to prevent the metabolic diseases. This review was aimed to update some research findings regarding the biological activities of the underutilized parts of mangosteen (pericarp and seed) along with phytochemical components. During this review, some information which are relevant to the study have been compiled using scientific literature from electronic search engines, including ScienceDirect, PubMed, Web of Science, Google Scholar, and other scientific electronic resources. Additional literature works were obtained from book chapters, books, websites, government reports, and other related sources. The underutilized part of mangosteen fruit is rich in xanthone derivatives as value-added constituents. The pericarp and seed also contain the derivatives of benzophenones, flavonoids, and anthocyanins. This study highlighted on the possible medicinal properties, especially for metabolic diseases such as obesity and lipid metabolism disorder, high blood pressure, diabetes along with its complication, and cancer. Besides, toxicological assessments were discussed to ensure the safety and trust of the consumers.

INTRODUCTION

In recent years, non-communicable diseases (NCDs) have become the major cause of mortality in both developing and developed countries (Saklayen, 2018). Among all these NCDs, the metabolic diseases have been associated with life behavior (Kaur, 2014; Saklayen, 2018). Metabolic syndromes are a cluster of metabolic abnormalities, which can be marked by the interconnectedness of physiological, biochemical, clinical, and metabolic factors, so that they can promote various diseases such as obesity, hypertension, hyperglycemic, cancer, and other diseases (Kaur, 2014; Saklayen, 2018; Srikanthan *et al*., 2016).

Nowadays, the lifestyle behavior has shifted toward a more health awareness behavior such as a consumption of value-added products and health-boosting foods and drinks containing some bioactive compounds mainly phenolics and flavonoids having potential activities to lower the risk of diseases (Bigliardi and Galati, 2013; Dell'agli *et al*., 2013; Siró *et al*., 2008). One of the common food supplements is derived from the plant bioactive compounds present in leaves, fruit, bark, and other parts (Cencic and Chingwaru, 2010). *Garcinia mangostana* L. is a potential plant which has evidence of broad pharmacological activities (Obolskiy *et al*., 2009).

*Corresponding Author
Abdul Rohman, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.
E-mail: abdulrohmanugm @ gmail.com

Garcinia mangostana L. or mangosteen, belonging to the genus *Garcinia* (family: Clusiaceae), is an evergreen and lactiferous tree (Lim, 2012; The Plant List, 2013). It is a native to the Malay archipelago and distributed in the tropical area. The fruit is a berry, globose to subglobose, smooth, turning from pale green to pink to maroon to dark purple-black when ripe and has a size of approximately 4–7 cm in diameter (Fig. 1). Mangosteen fruit is usually eaten as dessert, which is well known as the queen of fruits. As a consequence, the waste of the pericarp and seed is abundance. Therefore, there are some research works on exploring health-beneficial of underutilized part of mangosteen in both pericarp and seed as food supplements (Ovalle-Magallanes *et al*., 2017). Many researchers have found a number of beneficial phytochemical constituents in both pericarp and seed of mangosteen plant including xanthones, benzophenones, flavonoids, and anthocyanins (Chin and Kinghorn, 2008; Lim, 2012). Xanthones are phytochemical constituents, which have many health benefits particularly for metabolic diseases (Pedraza-Chaverri *et al*., 2008).

Some review articles existed in relation to mangosteen fruit. Rohman *et al*. (2019) explained the chemical composition and antioxidant studies of the underutilized part of mangosteen. However, this review failed to explore the other effects of mangosteen in preventing the metabolic disorders such as lipid metabolism disorder, high blood pressure, diabetes, and cancer. Gutierrez-Orozco and Failla (2013) discussed the biological activities of xanthones (as main component in mangosteen) as antioxidant, antiproliferative, proapoptotic, anti-inflammatory, and anticarcinogenic activities along with molecular mechanism underlying these biological activities. A similar review also existed related to biological activities of xanthones isolated from mangosteen pericarp as antineoplastic agent, antioxidant, antiproliferation, and induction of apoptosis (Chen *et al*., 2018). Both the review articles did not inform the other components such as flavonoid and phenolics contributing the biological activities. Besides, this review also did not explain the safety issues related to xanthone derivatives.

Figure 1. Photographs of *Garcinia mangostana* L. fruit (a) fresh, (b) dried.

Wang *et al*. (2017) discussed the biological activities of compounds belonging to isoprenylated xanthones present in mangosteen pericarp. The numerous *in vitro* and *in vivo* studies possess diverse pharmacological activities, such as antibacterial, antifungal, antimalarial, anticarcinogenic, and antiatherogenic activities as well as neuroprotective properties in Alzheimer's disease. However, this article did not explore wider metabolic disorders such as lipid disorders and diabetic diseases. In this review, we provided the current reports on the phytochemical and pharmacological progress, especially for metabolic diseases and toxicological study to convince the consumers and patients. More importantly, this study was expected to promote researchers and stakeholders to develop further investigations of the underutilized part of mangosteen as food supplements.

PHYTOCHEMICAL PROPERTIES

The previous investigations on phytochemical of the underutilized part of mangosteen fruit revealed the abundance of xanthones, benzophenones, flavonoids, and anthocyanins (Chin and Kinghorn, 2008; Lim, 2012). Health benefits of the underutilized part of this fruit are focussed on xanthones, particularly α-, β-, and γ-mangostins, garcinone E, 8-deoxygartanine, and gartanine having the chemical structures as shown in Figure 2 (Pedraza-Chaverri *et al*., 2008). Besides that, xanthones have been isolated from pericarp, whole fruit, heartwood, stem bark, root bark, and leaves of mangosteen (Pedraza-Chaverri *et al*., 2008). In the present profile, all known secondary metabolites of the underutilized part of mangosteen fruit found in the literature are shown in Table 1.

HEALTH BENEFITS FOR METABOLIC DISEASES

Several publications reported the biological activities of the underutilized part of mangosteen, including anti-obesity and lipid metabolism disorder, antihypertensive, antidiabetic, and anticancer activities (Table 2).

Obesity and lipid metabolism disorder

Obesity is an abnormality of adipose tissue due to its excessive secretion of adipokines having a major contribution in the pathophysiology of diabetes mellitus, insulin resistance, dyslipidemia, hypertension, and atherosclerosis (Redinger, 2007). There are numerous pharmacological activities related to anti-obesity and lipid metabolism disorder, including anti-adipogenic, antihyperlipidemic, anti-inflammatory, and antioxidant activity (Adiputro *et al*., 2013; Liu *et al*., 2014; Lusiana *et al*., 2015). Besides, the molecular mechanisms are also proposed, such as decreasing the induction by lipopolysaccharide of inflammatory genes, preventing the insulin resistance in human adipocytes, inhibiting the pancreatic lipase and α-amylase, and activating monophosphate-activated

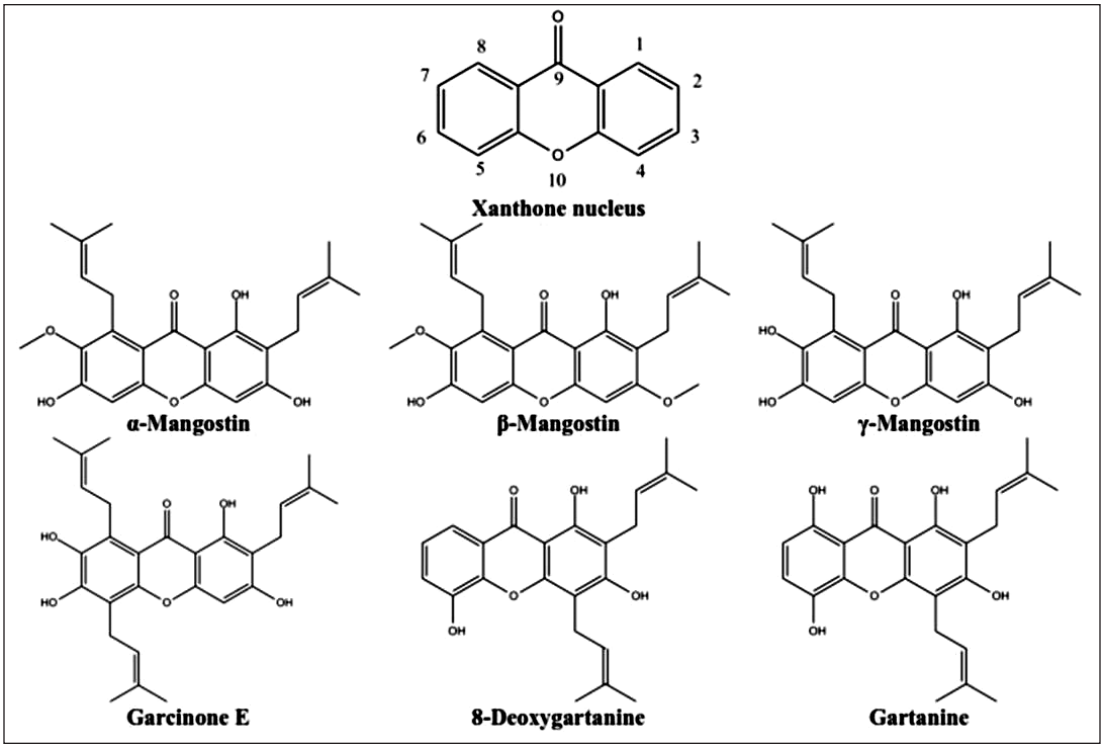


Figure 2. Xanthone nucleus and structure belong to some xanthones of *G. mangostana* L. (approximately here).

protein kinase (AMP)-activated protein kinase (Bumrungpert *et al*., 2009; Chae *et al*., 2016a; 2016b; Ketut *et al*., 2016).

The ethanolic extract of mangosteen pericarp at a dose of 200 mg/kgBW can increase HDL level; meanwhile, at a dose of 400 mg/kgBW, it can decrease cholesterol, triglyceride, and low-density lipoprotein (LDL) (Adiputro *et al*., 2013). Lusiana *et al*. (2015) reported that the ethanolic extract of mangosteen pericarp possesses a better anti-adipogenic in human liver carcinoma cells (HepG2) cell than other xanthones, such as α- and γ-mangostin, garcinone C, and garcinone D by inhibiting triglyceride and cholesterol synthesis. Besides, the extract of fruit pericarp has a better potency to inhibit pancreatic lipase and α-amylase activity than that of α-mangostin. However, its activity was still lower than the standard active pharmaceutical ingredients of orlistat and acarbose (Ketut *et al*., 2016). Recently, Kusmayadi *et al*. (2019) also reported that mangosteen decreased total cholesterol levels due to the presence of xanthones having hypocholesterolemic activity capable of reducing cholesterol levels. During the cholesterol formation, there is a stage of squalene synthesis. The antioxidant compounds (xanthone derivatives) could inhibit the squalene synthesis, and thus, cholesterol formation could be decreased (Chomnawang *et al*., 2007).

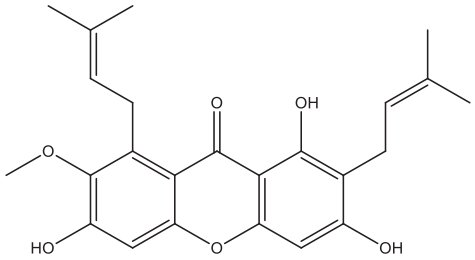
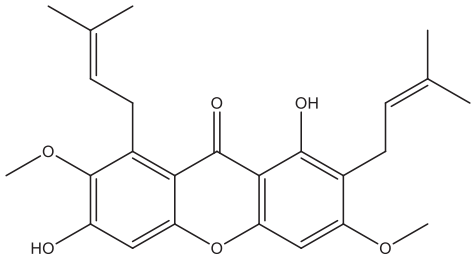
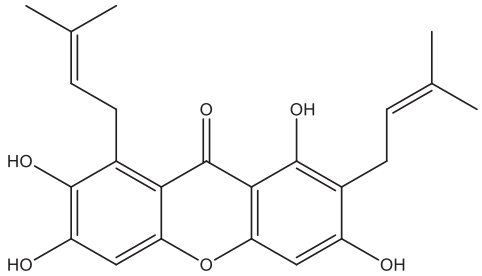
An *in vivo* study by Chae *et al*. (2016b) indicated that the ethanolic extract of mangosteen pericarp at 200 mg/kgBW decreased triglyceride, cholesterol, LDL, and free fatty acid levels. These extracts also exert anti-obesity by activating the hepatic AMP-activated protein kinase and Sirtuin 1 and by suppressing peroxisome proliferator-activated receptors (PPARγ) expression in the liver (Chae *et al*., 2016b). Thirteen xanthones isolated from mangosteen pericarp including α-, β-, and γ-mangostin, 1-isomangostin, gartanin, garcinone D, 9-hydroxycalabaxanthone, smeathxanthone A, tovophyllin A, 8-deoxygartanin, mangostanin, calocalabaxanthone, and 1,7-dihydroxy-3-methoxy-2-(3-methylbut-2-enyl) xanthen-9-one showed the inhibition of pancreatic lipase (Chae *et al*., 2016a). This study also showed that α-mangosten was found to possess the most potent lipase inhibitor with an IC_{50} value of 5.0 μM; meanwhile, orlistat as positive control has an IC_{50} of 3.9 μM (Chae *et al*., 2016a). Besides, xanthones including α- and γ-mangostin attenuate LPS-mediated inflammation and insulin resistance in human adipocytes, possibly by inhibiting the activation of mitogen-activated protein kinase (MAPK), NF-κB, and activator protein (AP)-1 activity (Bumrungpert *et al*., 2009).

Reducing high blood pressure

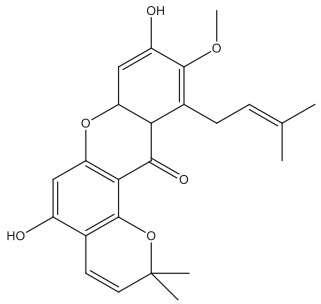
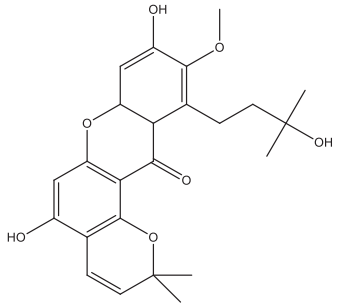
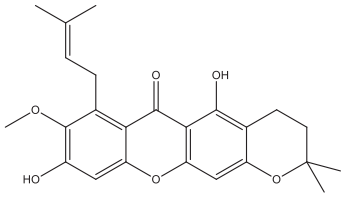
Hypertension is a main risk of cardiovascular disease, including ischemic heart disease, ultimately cardiac failure, coronary artery disease, artial fibrillation, and peripheral vascular disease (Boonprom *et al*., 2017; Slivnick and Lampert, 2019). Some research works have been proven that mangosteen pericarp has antihypertensive activity. The water extract of the pericarp at a dose of 200 mg/kgBW has the protective effect on nitro-L-arginine methyl ester (L-NAME)-induced hypertension and cardiovascular remodeling. This extract might prevent the oxidative stress induced by L-NAME and enhance the nitric oxide (NO) bioavailability via suppressing NADPH oxidase subunit $p47^{phox}$ expression. Furthermore, this extract can prevent inflammation development in L-NAME hypertensive rats by decreasing plasma tumor necrosis factor-α (TNF-α) and suppressing iNOS protein expression (Boonprom *et al*., 2017).

Another report showed that some isolated active compounds from mangosteen pericarp including aromadendrin-8-C-ß-D-glucopyranoside, maclurin-6-O-ß-D-glucopyranoside (rhodanthenone), and epicatechin can alleviate the excision of

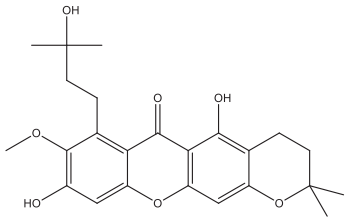
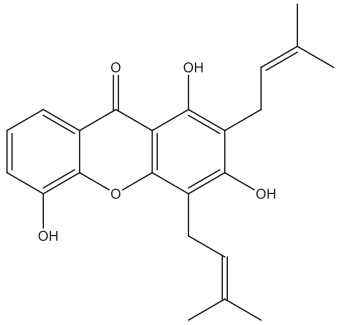
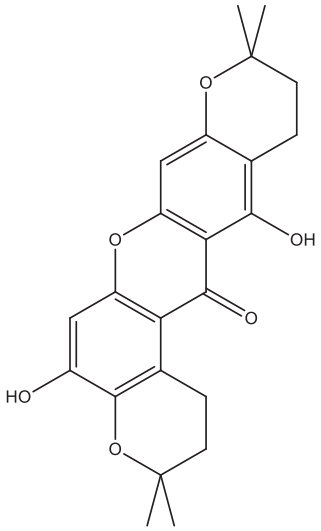
Table 1. Secondary metabolites contained in different parts of *Garcinia mangostana* L.

No.	Chemical compounds	Chemical structures	Underutilized parts	References
	Xanthones			
1	α-Mangostin		Pericarp; Seed	Gopalakrishnan *et al.* (1997)
2	β-Mangostin		Pericarp	Gopalakrishnan *et al.* (1997)
3	γ-Mangostin		Pericarp	Gopalakrishnan *et al.* (1997)
4	1,3,6,7-Tetrahydroxy-2,8(3-methyl-2-butenyl)xanthoneP1		Pericarp	Yu *et al.* (2007)
5	1,3,6,7-Tetrahydroxy-8-isoprenyl-9H-xanthen-9-one		Pericarp	Huang *et al.* (2001)
6	1,3,6,7-Tetrahydroxy-8-(3 methyl-2-buthenyl)-9H-xanthon-9-one		Pericarp	Huang *et al.* (2001)
7	1,3,6-Trihydroxy-7methoxy-2,8-(3-methyl-2butenyl)-xanthone P2		Pericarp	Yu *et al.* (2007)
8	1,3,7-Trihydroxy-2,8-di-(3-methylbut-2-enyl) xanthone		Pericarp	Mahabusarakam *et al.* (1987)
9	1,5-Dihydroxy-2-(3methylbut-2-enyl)-3methoxy-xanthone		Pericarp	Asai *et al.* (1995)
10	1,5-dihydroxy-2-isopentyl-3-methoxy-xanthone		Pericarp	Farnsworth and Bunyapraphatsara (1992)

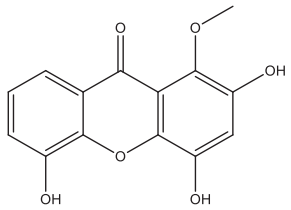
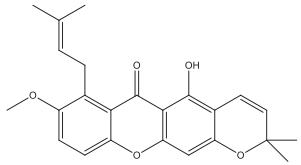
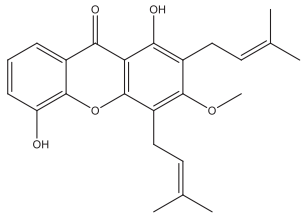
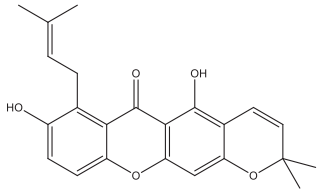
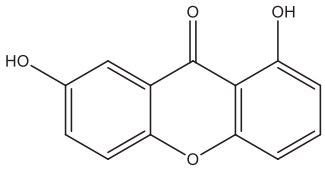
Continued

No.	Chemical compounds Xanthones	Chemical structures	Underutilized parts	References
11	1,5-Dihydroxy-2-isoprenyl-3-methoxyxanthone		Pericarp	Asai *et al*. (1995), Iinuma *et al*. (1996); Huang *et al*. (2001)
12	1,6-Dihydroxy-7-methoxy-8-isoprenyl-6',6'-dimethylpyrano(2',3':3,2) xanthone		Pericarp	Suksamrarn *et al*. (2003)
13	1,7-Dihydroxyxanthone		Pericarp	Iinuma *et al*. (1996)
14	1,7-Dihydroxy-2-(3-methylbut-2-enyl)-3methoxy-xanthone		Pericarp	Asai *et al*. (1995)
15	1,7-Dihydroxy-2-isopentyl-3-methoxy-xanthone		Pericarp	Farnsworth and Bunyapraphatsara (1992)
16	5,9-Dihydroxy-8-methoxy-2,2 dimethyl-7-isopre-nyl2H,6H-pyrano[3,2-b] xanthen-6-one		Pericarp	Sen *et al*. (1980)
17	1,7-Dihydroxy-2-isoprenyl-3-methoxyxanthone		Pericarp	Asai *et al*. (1995); Iinuma *et al*. (1996); Huang *et al*. (2001)
18	1-Isomangostin		Pericarp	Farnsworth and Bunyapraphatsara (1992); Jung *et al*. (2006); Mahabusarakam and Wiriyachitra (1987); Peres *et al*. (2000); Vieira and Kijjoa (2005).
19	1-Isomangostin hydrate		Pericarp	Mahabusarakam and Wiriyachitra (1987); Peres *et al*. (2000);
20	3-Isomangostin		Pericarp	Mahabusarakam *et al*. (1987); Huang *et al*. (2001)

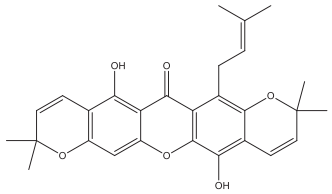
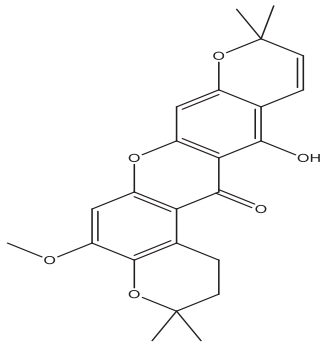
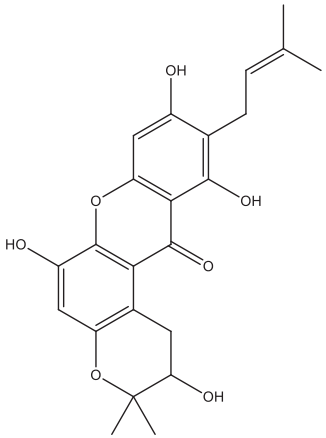
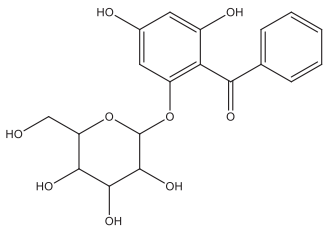
Continued

No.	Chemical compounds Xanthones	Chemical structures	Underutilized parts	References
21	3-Isomangostin hydrate		Pericarp	Mahabusarakam *et al.* (1987)
22	2-Isoprenyl-1,7-dihydroxy-3 methoxyxanthone		Pericarp	Matsumoto *et al.* (2003)
23	2,7-di-Isoprenyl-1,3,8-trihydroxy-4-methyl xanthone		Pericarp	Gopalakrishnan and Balaganesan (2000)
24	2,8-di-Isoprenyl-7-carboxy-1,3,-trihydroxy-4-methyl xanthone		Pericarp	Gopalakrishnan and Balaganesan (2000)
25	2,8-Diisoprenyl-7-carboxy-1,3 dihydroxyxanthone		Pericarp	Gopalakrishnan and Balaganesan (2000)
26	2-(γ,γ-Dimethylallyl)-1,7dihydroxy-3-methoxyxanthone		Pericarp	Farnsworth and Bunyapraphatsara (1992)
27	8-Deoxygartanin		Pericarp	Chairungsrilerd *et al.* (1998b); Gopalakrishnan *et al.* (1997); Gopalakrishnan and Balaganesan (2000); Suksamrarn *et al.* (2006); Vieira and Kijjoa (2005)
28	8-Hydroxycudraxanthone		Pericarp	Jung *et al.* (2006)
29	BR-Xanthone A		Pericarp	Balasubramanian and Rajagopalan (1988)

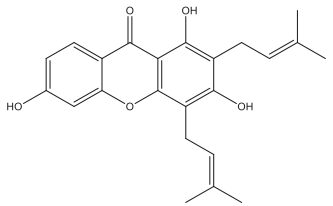
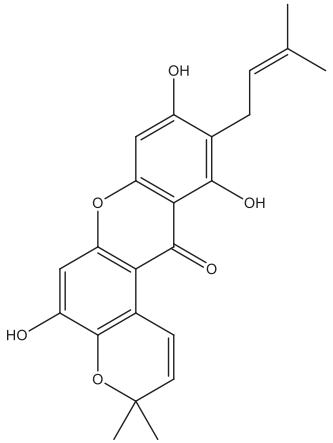
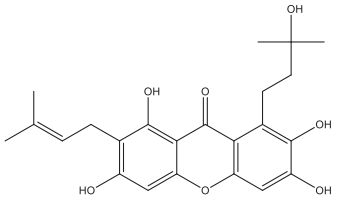
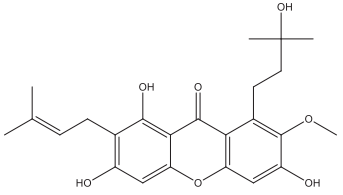
Continued

No.	Chemical compounds Xanthones	Chemical structures	Underutilized parts	References
30	BR-Xanthone B		Pericarp	Balasubramanian and Rajagopalan (1988)
31	Calabaxanthone		Pericarp	Mahabusarakam *et al.* (1987)
32	Caloxanthone A		Pericarp	Iinuma *et al.* (1996)
33	Cudraxanthone G		Pericarp	Jung *et al.* (2006)
34	Demethylcalabaxanthone		Seed	Mahabusarakam and Wiriyachitra (1987); Suksamrarn *et al.* (2003)
35	2-(γ,γ -Dimethylallyl)1,7-dihydroxy-3-methoxyxanthone		Pericarp	Mahabusarakam *et al.* (1987)
36	2,8bis(γ, γ-Dimethylallyl)-1,3,7-trihydroxyxanthone		Pericarp	Mahabusarakam *et al.* (1987)
37	Esmeatxanthone A		Pericarp	Jung *et al.* (2006)
38	Euxanthone		Pericarp	Gopalakrishnan *et al.* (1997)

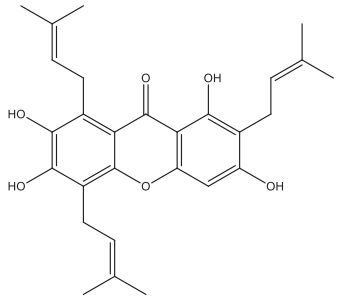
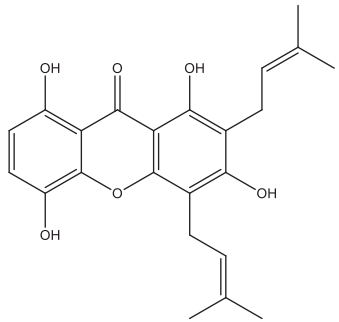
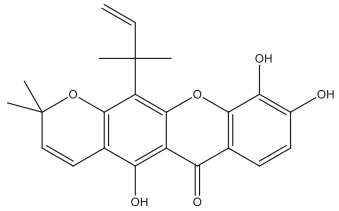
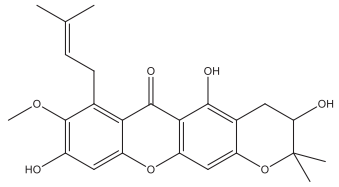
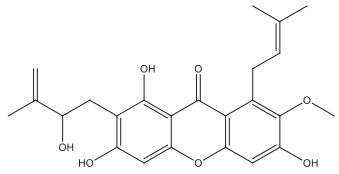
Continued

No.	Chemical compounds Xanthones	Chemical structures	Underutilized parts	References
39	Garcimangosone A		Pericarp	Huang *et al.* (2001)
40	Garcimangosone B		Pericarp	Huang *et al.* (2001); Jung *et al.* (2006); Vieira and Kijjoa (2005)
41	Garcimangosone C		Pericarp	Huang *et al.* (2001); Vieira and Kijjoa (2005)
42	Garcimangosone D		Pericarp	Huang *et al.* (2001)

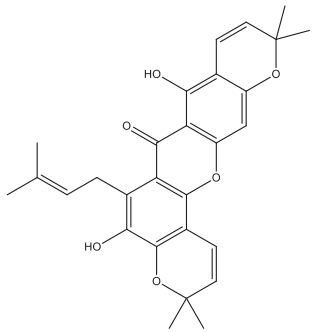
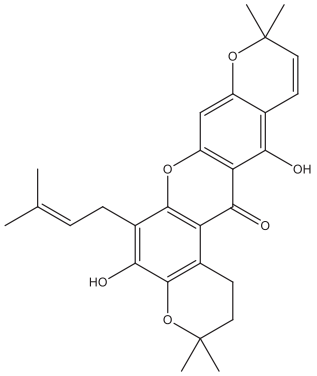
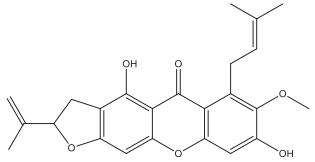
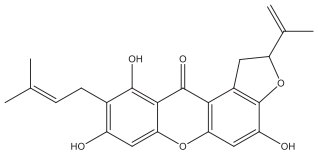
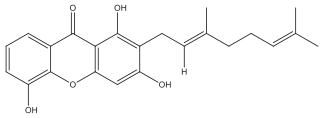
Continued

No.	Chemical compounds Xanthones	Chemical structures	Underutilized parts	References
43	Garcinone A		Pericarp	Sen *et al.* (1982)
44	Garcinone B		Pericarp	Farnsworth and Bunyapraphatsara (1992); Suksamrarn *et al.* (2002, 2006).
45	Garcinone C		Pericarp	Sen *et al.* (1982)
46	Garcinone D		Pericarp	Farnsworth and Bunyapraphatsara (1992); Jung *et al.* (2006); Suksamrarn *et al.* (2003; 2006); Vieira and Kijjoa (2005)

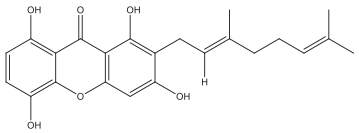
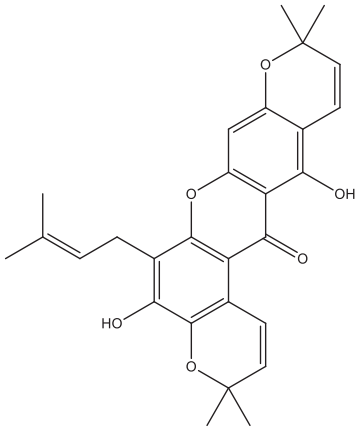
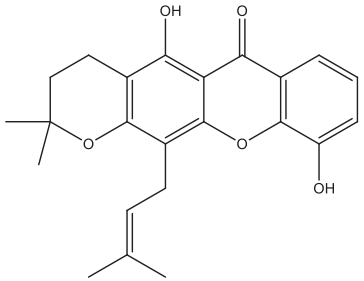
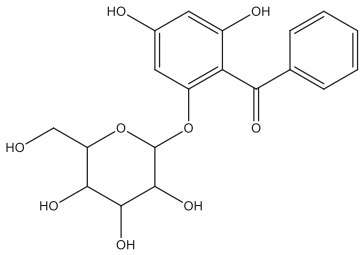
Continued

No.	Chemical compounds Xanthones	Chemical structures	Underutilized parts	References
47	Garcinone E		Pericarp	Asai *et al.* (1995); Chairungsrilerd *et al.* (1998a); Jung *et al.* (2006); Matsumoto *et al.* (2003); Peres *et al.* (2000); Suksamrarn *et al.* (2006); Vieira and Kijjoa (2005)
48	Gartanin		Pericarp	Chairungsrilerd *et al.* (1998a); Gopalakrishnan *et al.* (1997); Jung *et al.* (2006); Mahabusarakam and Wiriyachitra (1987); Peres *et al.* (2000); Suksamrarn *et al.* (2006); Vieira and Kijjoa (2005)
49	Macluraxanthone		Pericarp	Iinuma *et al.* (1996)
50	Mangostanin		Pericarp	Harrison (2002); Suksamrarn *et al.* (2003); Vieira and Kijjoa (2005)
51	Mangostanol		Pericarp	Chairungsrilerd (1998a); Suksamrarn *et al.* (2002, 2003); Huang *et al.* (2001)
52	Mangostenol		Pericarp	Suksamrarn *et al.* (2002); Vieira and Kijjoa (2005)

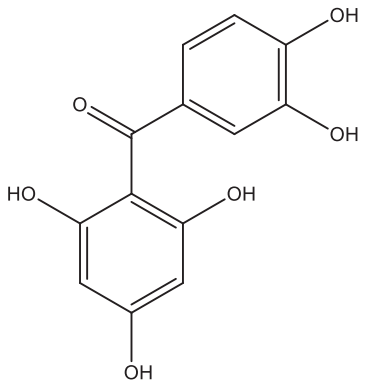
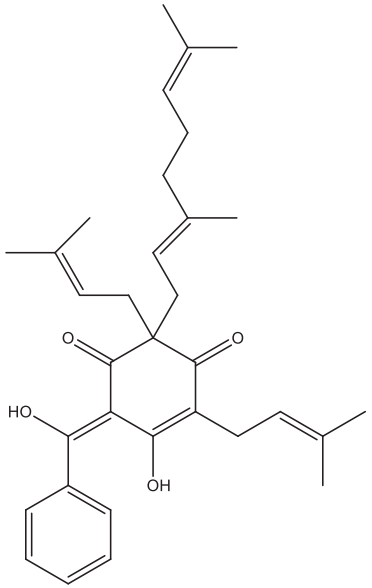
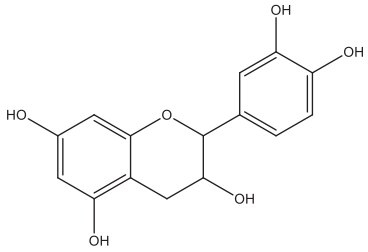
Continued

No.	Chemical compounds Xanthones	Chemical structures	Underutilized parts	References
53	Mangostenone A		Pericarp	Suksamrarn *et al.* (2002); Vieira and Kijjoa (2005)
54	Mangostenone B		Pericarp	Suksamrarn *et al.* (2002); Vieira and Kijjoa (2005)
55	Mangostenone F		Pericarp	Ryu *et al.* (2010)
56	Mangostenone G		Pericarp	Ryu *et al.* (2010)
57	Mangostinone		Pericarp	Asai *et al.* (1995); Jung *et al.* (2006); Matsumoto *et al.* (2003); Suksamrarn *et al.* (2006); Vieira and Kijjoa (2005)
58	Mangostingone [7-methoxy-2-(3- isoprenyl)-8-(3-methyl-2-oxo-3-buthenyl)-1,3,6-trihydroxyxanthone		Pericarp	Jung *et al.* (2006)
59	1-Methoxy-2,4,5-trihydroxyxanthone		Pericarp	Balasubramanian and Rajagopalan (1988)

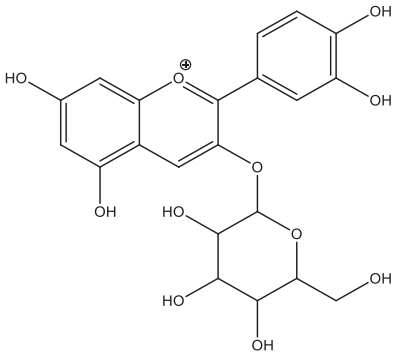
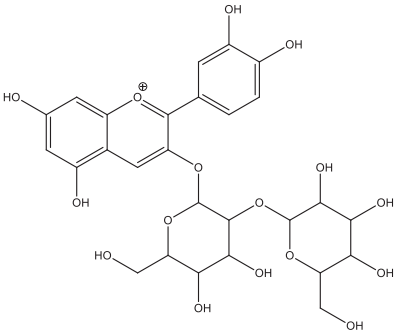
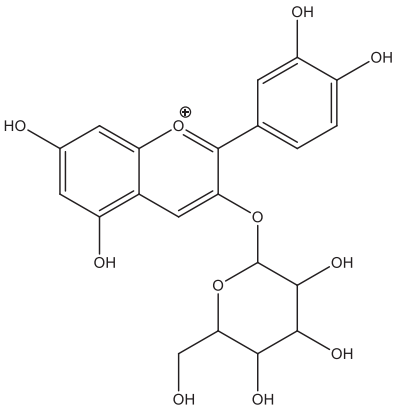
Continued

No.	Chemical compounds	Chemical structures	Underutilized parts	References
	Xanthones			
60	Smeathxanthone A		Pericarp	Jung *et al.* (2006)
61	Tovophyllin A		Pericarp	Jung *et al.* (2006)
62	Tovophyllin B		Pericarp	Suksamrarn *et al.* (2002); Vieira and Kijjoa (2005)
63	Trapezifolixanthone		Pericarp	Suksamrarn *et al.* (2002); Vieira and Kijjoa (2005)
64	Xanthone I		Seed	Chin and Kinghorn (2008)
	Benzophenons			
1	Garcimangosone D		Pericarp	Huang *et al.* (2001)

Continued

No.	Chemical compounds	Chemical structures	Underutilized parts	References
	Xanthones			
2	Maclurin		Pericarp	Farnsworth and Bunyapraphatsara (1992); Mahabusarakam and Wiriyachitra (1987)
3	Kolanone		Pericarp	Farnsworth and Bunyapraphatsara (1992)
	Flavonoids			
1	Epicatehin		Pericarp	Chairungsrilerd *et al*. (1998b); Suksamrarn *et al*. (2002); Yu *et al*. (2007)

Continued

No.	Chemical compounds Xanthones	Chemical structures	Underutilized parts	References
	Anthocyanins			
1	Chrysanthemin		Pericarp	Farnsworth and Bunyapraphatsara (1992)
2	Cyanidin-3-O-sophoroside		Pericarp	Farnsworth and Bunyapraphatsara (1992)
3	Cyanidin-glucoside		Pericarp	Lim (2012)
4	Cyanidin-glucoside-pentoside		Pericarp	Lim (2012)

Continued

Table 2. Pharmacological activities of *G. mangostana* L.

Pharmacological activities	Remarks	References
Anti-obesity	The ethanolic extract of pericarp at a dose of 200 mg/kgBW can increase HDL level; meanwhile, at a dose of 400 mg/kgBW, it can decrease cholesterol, tryglyceride, and LDL	Adiputro *et al*. (2013)
	The ethanolic extract of pericarp possesses the better anti-adipogenic in HepG2 cell than other xanthones such as α-mangostin, γ-mangostin, garcinone C, and garcinone D by inhibiting triglyceride and cholesterol synthesis.	Lusiana *et al*. (2015)
	The ethanolic extract of pericarp also has a better potency to inhibit pancreatic lipase and α-amylase activity than α-mangostin.	Ketut *et al*. (2015)
	Mangosteen decreased total cholesterol levels.	Kusmayadi *et al*. (2019)
	The ethanolic extract of pericarp at 200 mg/kgBW decreased triglyceride, cholesterol, LDL, and free fatty acid levels. These extracts also exert antiobesity by activating the hepatic AMP-activated protein kinase and Sirtuin 1 and by suppressing PPARγ expression in the liver.	Chae *et al*. (2016b)
	Thirteen xanthones isolated from mangosteen pericarp including α-mangostin, β-mangostin, γ-mangostin, 1-isomangostin, gartanin, garcinone D, 9-hydroxycalabaxanthone, smeathxanthone A, tovophyllin A, 8- deoxygartanin, mangostanin, calocalabaxanthone, and 1,7-dihydroxy-3-methoxy-2-(3-methylbut-2-enyl) xanthen-9-one showed the inhibition of pancreatic lipase. This study also showed that α-mangostin was found to possess the most potent lipase inhibitor with an IC_{50} value of 5.0 μM.	Chae *et al*. (2016a)
	Xanthones including α- and γ-mangostin attenuate LPS-mediated inflammation and insulin resistance in human adipocytes, possibly by inhibiting the activation of mitogen-activated protein kinase (MAPK), NF-κB, and activator protein (AP)-1 activity.	Bumrungpert *et al*. (2009)
Antihypertension	The water extract of the pericarp at a dose of200 mg/kgBW has the protective effect on L-NAME (nitro-L-arginine methyl ester)-induced hypertension, prevent the oxidative stress, enhance nitric oxide (NO) bioavailability via suppressing NADPH oxidase subunit $p47^{phox}$ expression, and prevent inflammation by decreasing plasma TNF-α and suppressing iNOS protein expression.	Boonprom *et al*. (2017)
	Isolated active compounds from pericarp including aromadendrin-8-C-ß-D-glucopyranoside, maclurin-6-O-ß-D-glucopyranoside, and epicatechin can alleviate the excision of vasoconstriction in the aorta and vasodilation in pre-contracted aorta through vasodilation mechanism.	Abdallah *et al*. (2016)
	γ-Mangostin possesses antihypertensive via NO-cGMP pathway, inhibition of extracellular Ca^{2+}, influx and activation of K^{+} channels, and prevention of vasoconstriction in the rat aorta.	Tep-Areenan and Suksamrarn (2012)
Antidiabetic	The juice of pericarp at 110 mg/kgBW showed glucose level reduction and pancreatic histology improvement due to streptozotocin induction.	Kurniawati *et al*. (2014)
	The ethanolic extract of pericarp on type-2 diabetic mice showed an ability to reduce fasting blood cholesterol level and lipid peroxidation, i.e., malondialdehyde level.	Husen *et al*. (2017)
	The ethanolic extract of pericarp significantly reduced triglyceride, total cholesterol, LDL, VLDL, SGOT, SGPT, urea, and creatinine as well as increased high-density lipoprotein (HDL), total protein, and the population of β-cels in the diabetic rats.	Taher *et al*. (2016)
	The hexane, dichloromethane, and methanol extracts of pericarp have a molecular mechanism on inhibiting α-amylase; meanwhile, hexane extracts can also be able to inhibit CETP.	Mishra *et al*. (2016)
	The oligomeric proanthocyanidin fractions have highly potent as α-amylase inhibitor with inhibitory activity expressed by an IC_{50} value of 5.4 μg/mL.	Loo and Huang (2007)
	Proanthocyanidin A2 also possesses to inhibit α-amylase activity with an IC_{50} value of 3.46 μM.	Tran *et al*. (2016)
	The ethanolic extract of the pericarp of the fruit has a potency for retinopathy diabetes by reducing plasma creatinin level and ameliorating renal proximal tubules in streptozotocin-induced diabetic mice.	Ansori *et al*. (2019)
	α-Mangostin also prevents diabetes complications on sexual dysfunction in male streptozotocin-induced diabetic rats due to capability as antioxidant on the testis and epididymis. α-Mangostin also improves sperm counts, motile sperms, viable sperms, hypo-osmotic swelling tail coiled sperms, and serum testosterone and also reduces sperm malformations.	Nelli *et al*. (2013)
	The clinical study of the pulp extract has improved significant insulin sensitivity with no side effects attributable to this treatment.	Watanabe *et al*. (2018)

Continued

Pharmacological activities	Remarks	References
Anti-cancer	The methanolic extract of the pericarp showed strong antiproliferation, potent antioxidation, and induction of apoptosis on human breast cancer SKBR3 cell lines.	Moongkarndi *et al*. (2004)
	Panaxanthone, which consists of approximately α-mangostin (80%) and γ-mangostin (20%), induces apoptosis, inhibits DNA synthesis and cell cycle arrest in the G1-phase, and reduces angiogenesis in mammary cancer-induced mice.	Doi *et al*. (2009)
	α-Mangostin isolated from the pericarp fruit significantly decreased phospho-Akt-threonine 308 (Thr308) which plays on cell proliferation, anti-apoptotic cell death, angiogenesis, and metastasis. Besides that, α-mangostin also induced mitochondrial-mediated apoptosis and G1-phase arrest and S-phase suppression in the cell cycle.	Shibata *et al*. (2011)
	γ-Mangostin is the most potent compound on SK-BR-3 breast cancer cell lines.	Balunas *et al*. (2008)
	Epicatechin and 1,3,6,7-tetrahydroxy-2,8-(3methyl-2-butenyl)xanthone showed potent cytotoxicities on MCF-7 human breast cancer cell lines.	Yu *et al*. (2009)
	Garcinone E showed considerable cytotoxic in MCF-7 cell line.	Mohamed *et al*. (2017)
	α-Mangostin could upregulate the MAPK/ERK, c-Myc/Max, and p53 cell signaling pathways on HCT 116 colorectal carcinoma cells.	Aisha *et al*. (2012)
	α-Mangostin showed a growth inhibition on human colon cancer DLD-1 cell lines.	Akao *et al*. (2008)
	α-Mangostin indicated the effective effect for inducing apoptotic cell death on COLO 205 through a link between extrinsic and intrinsic pathways.	Watanapokasin *et al*. (2011)
	γ-Mangostin indicated anticancer activity and induced apoptosis on HT29 colorectal adenocarcinoma cells.	Chang and Yang, (2012)
	Epicatechin and 1,3,6,7-tetrahydroxy-2,8-(3methyl-2-butenyl)xanthone showed potent cytotoxicities on human colon cancer cell lines.	Yu *et al*. (2009)
	α-Mangostin can induce apoptosis and inhibit the proliferation of four prostate cancer cell lines, i.e., LNCaP, 22Rv1, DU145, and PC-3.	Li *et al*. (2013)
	α-Mangostin showed an apoptosis induction and tumor growth suppression on human prostate cancer cell lines.	Li *et al*. (2014)
	The ethanolic extract of pericarp significantly induced apoptosis on two skin cancer cell lines including human squamous cell carcinoma A-431 and melanoma SK-MEL-28 lines.	Wang *et al*. (2012)
	Three xanthone compounds such as α-mangostin, γ-mangostin, and 8-deoxygartanin exhibited a significant cytotoxicity on human melanoma SK-MEL-28 cell line. α-Mangostin is a potent compound in apoptotic induction via caspase activation and disruption of mitochondrial membrane pathways.	Wang *et al*. (2011)
	Mangostana xanthone VII as an isolated compound from the pericarp showed a moderate cytotoxic activity on epithelial lung carcinoma A549.	Ibrahim *et al*. (2017)
	Seven isolated compounds from the pericarp fruit including 1,3,7-trihydroxy-2-(3-methyl-2-butenyl)-8-(3-hydroxy-3-methylbutyl)-xanthone, 1,3,8-trihydroxy-2-(3-methyl-2-butenyl)-4(3hydroxy-3-methylbutanoyl)-xanthone, garcinones C and D, gartanin, xanthone I, and γ mangostin showed the significant cytotoxic activities on various human cancer cell lines, namely, human nasopharyngeal carcinoma cell line (CNE1, CNE2, SUNE1, and HONE1), human lung cancer cell line (A549 and GLC82), human breast cancer cell line (MCF-7), and human hepatic cancer cell line (Bel-7402).	Xu *et al*. (2014)
	γ-Mangostin showed a potent antiproliferative activity and apoptosis induction on human brain tumors including U87 MG and GBM 8401.	Chang *et al*. (2010)
	α-Mangostin has a potential efficacy on four human pancreatic cancer (PL-45, PANC1, BxPC3, and ASPC1) through inducing apoptosis, inhibiting the expression level of pNF-κB/p65Ser552, pStat3Ser727, pStat3Tyr705, MMP9, cyclin D1, gp130, and biomarkers of cell proliferation (Ki-67 and PCNA, and increasing the expression of tissue inhibitor of metalloproteinase 1.	Hafeez *et al*. (2014)

vasoconstriction in the aorta and vasodilation in precontracted aortae through vasodilation mechanism (Abdallah *et al*., 2016). Besides, γ-mangostin possesses antihypertensive via NO-cGMP pathway, inhibition of extracellular Ca^{2+}, influx and activation of K^{+} channels, and prevention of vasoconstriction in the rat aorta.

Antidiabetic activity

Diabetes mellitus (DM) is one of the most common chronic endocrine and metabolic diseases which become a main problem to human health around the world (Ighodaro *et al*., 2018; Maleki *et al*., 2019). DM is characterized by insufficient insulin secretion, resistance to the action of insulin, or both. DM is marked by hyperglycemia as clinical manifestation and can lead to complications known as neuropathy, nephropathy, retinopathy, cardiovascular, cerebrovascular, and peripheral vascular disease (DiPiro *et al*., 2008; Glasheen *et al*., 2017; Yeung *et al*., 2018). Recently, there are numerous reports on the antidiabetic activity of extracts and isolated compounds from mangosteen.

An *in vivo* study of the juice of mangosteen pericarp at 110 mg/kgBW showed a glucose level reduction and pancreatic histology improvement due to streptozotocin induction (Kurniawati *et al*., 2014). The investigation of ethanolic extract of the pericarp of the fruit on type-2 diabetic mice showed an ability to reduce fasting blood cholesterol level and lipid peroxidation, i.e., malondialdehyde level (Husen *et al*., 2017). The ethanolic extract of the pericarp of the fruit also significantly reduced triglyceride, total cholesterol, LDL, very low-density lipoprotein (VLDL), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), urea, and creatinine as well as increased high-density lipoprotein (HDL), total protein, and the population of β-cells in the diabetic rats (Taher *et al*., 2016).

Mishra *et al.* (2016) investigated that hexane, dichloromethane, and methanol extracts of mangosteen pericarp have a molecular mechanisms on inhibiting α-amylase; meanwhile, hexane extracts can also be able to inhibit cholesteryl ester transferase protein (CETP). Loo and Huang (2007) demonstrated that oligomeric proanthocyanidin fractions have an highly potent α-amylase inhibitor with inhibitory activity expressed by an IC_{50} value of 5.4 μg/ml, whereas acarbose as the positive control has an IC_{50} value of 5.2 μg/mL. Besides, proanthocyanidin A2 also possesses to inhibit α-amylase activity with an IC_{50} value of 3.46 μM (Tran *et al*., 2016).

Diabetic complications were also studied including retinopathy diabetes and sexual dysfunction. The ethanolic extract of the pericarp of the fruit has a potency for retinopathy diabetes by reducing plasma creatinin level and ameliorating renal proximal tubules in streptozotocin-induced diabetic mice (Ansori *et al*., 2019). Besides that, α-mangostin also prevents diabetes complications on sexual dysfunction in male streptozotocin-induced diabetic rats. It is suggested that α-mangostin has a capability as antioxidant on the testis and epididymis. Alfa-mangostin also improves sperm counts, motile sperms, viable sperms, hypo-osmotic swelling tail-coiled sperms, and reduced sperm malformations. Besides, α-mangostin showed the increasing level of serum testosterone (Nelli *et al*., 2013).

Insulin-sensitizing treatments are known to be effective to prevent diabetes and to induce weight loss. There is a wide association between insulin resistance and obesity/type 2 diabetes (T2DM), and obesity and T2DM are also associated with increased inflammation (Romeo *et al*., 2012). The clinical study has reported that mangosteen has improved a significant insulin sensitivity with no side effects attributable to this treatment, suggesting a possible supplementary role of mangosteen extracts in the treatment of obesity, insulin resistance, and inflammation (Watanabe *et al*., 2018).

Anticancer activity

Several studies have been designed to examine the anticancer activity of both extracts and isolated compounds from the underutilized part of mangosteen fruit. The methanolic extract of the pericarp fruit showed strong antiproliferation, potent antioxidation, and induction of apoptosis on human breast cancer SKBR3 cell lines (Moongkarndi *et al*., 2004). Panaxanthone, which consists of approximately α-mangostin (80%) and γ-mangostin (20%), induces apoptosis, inhibits DNA synthesis and cell cycle arrest in the G1-phase, and reduces angiogenesis in mammary cancer-induced mice (Doi *et al*., 2009). The α-mangostin isolated from the pericarp fruit significantly decreased phospho-Akt-threonine 308 (Thr308), which plays a vital role on cell proliferation, antiapoptotic cell death, angiogenesis, and metastasis. Besides that, α-mangostin also induced mitochondrial-mediated apoptosis and G1-phase arrest and S-phase suppression in the cell cycle (Shibata *et al*., 2011). Balunas *et al*. (2008) reported that γ-mangostin is the most potent compounds among 12 xanthones from α-mangostin pericarp on SK-BR-3 breast cancer cell lines. On the other hand, epicatechin and 1,3,6,7-tetrahydroxy-2,8-(3methyl-2-butenyl) xanthone showed potent cytotoxicities on human breast cancer cell line (MCF)-7 human breast cancer cell lines (Yu *et al*., 2009). Garcinone E also showed considerable cytotoxic in MCF-7 cell line (Mohamed *et al*., 2017).

The chemical constituents from the underutilized part of mangosteen also revealed the promising agent as colon anticancer. α-mangostin could upregulate the MAPK/ extracellular signal-regulated kinase (ERK), c-Myc/Max, and p53 cell signaling pathways on HCT 116 colorectal carcinoma cells (Aisha *et al*., 2012). Besides, α-mangostin also showed a growth inhibition on human colon cancer DLD-1 cell lines (Akao *et al*., 2008). Besides, α-mangostin also indicated the effective effect for inducing apoptotic cell death on COLO 205 through a link between extrinsic and intrinsic pathways (Watanapokasin *et al*., 2011). γ-mangostin also indicated anticancer activity and induced apoptosis on HT29 colorectal adenocarcinoma cells (Chang and Yang, 2012). Other compounds such as epicatechin and 1,3,6,7-tetrahydroxy-2,8-(3methyl-2-butenyl) xanthone showed potent cytotoxicities on human colon cancer cell lines (Yu *et al*., 2009).

The α-mangostin has been reported to induce apoptosis and inhibit the proliferation on four prostate cancer cell lines (LNCaP, 22Rv1, DU145, and PC-3) (Li *et al*., 2013). Besides that, α-mangostin also showed an apoptosis induction and tumor growth suppression on human prostate cancer cell lines (Li *et al*., 2014). On another cell type, the ethanolic extract of mangosteen pericarp significantly induced apoptosis on two skin cancer cell lines including human squamous cell carcinoma A-431 and melanoma SK-MEL-28 lines (Wang *et al*., 2012). Three xanthone compounds such as α-mangostin, γ-mangostin, and 8-deoxygartanin exhibited a significant cytotoxicity on human melanoma SK-MEL-28 cell

line. The α-mangostin is a potent compound in apoptotic induction via caspase activation and disruption of mitochondrial membrane pathways (Wang *et al*., 2011).

Mangostanaxanthone VII as an isolated compound from the pericarp of mangosteen showed a moderate cytotoxic activity on epithelial lung carcinoma A549 (Ibrahim *et al*., 2017). Seven isolated compounds from the pericarp fruit including 1,3,7-trihydroxy-2-(3-methyl-2-butenyl)-8-(3-hydroxy-3-methylbutyl)-xanthone, 1,3,8-trihydroxy-2-(3-methyl-2-butenyl)-4(3-hydroxy-3-methylbutanoyl)-xanthone, garcinones C and D, gartanin, xanthone I, and γ mangostin showed the significant cytotoxic activities on various human cancer cell lines, namely. human nasopharyngeal carcinoma cell line (CNE1, CNE2, SUNE1, and HONE1), human lung cancer cell line (A549 and GLC82), human breast cancer cell line (MCF-7), and human hepatic cancer cell line (Bel-7402) (Xu *et al*., 2014).

The γ-mangostin showed a potent antiproliferative activity and apoptosis induction on human brain tumors including U87 MG and GBM 8401 (Chang *et al*., 2010). On the other hand, α-mangostin suggested a potential efficacy on four human pancreatic cancers (PL-45, PANC1, BxPC3, and ASPC1). The mechanisms underlying these efficacies are through inducing apoptosis, inhibiting the expression level of pNF-κB/p65Ser552, pStat3Ser727, pStat3Tyr705, MMP9, cyclin D1, gp130, and biomarkers of cell proliferation (Ki-67 and proliferating cell nuclear antigen (PCNA), and increasing the expression of tissue inhibitor of metalloproteinase 1 (Hafeez *et al*., 2014).

Toxicological Studies

The toxicological studies are needed to assure the safety of mangosteen extracts; therefore, some reports on the safety of the underutilized part of mangosteen have been highlighted. The acute toxicity at the doses of 1.0, 2.0, and 3.0 g/kgBW of mangosteen pericarp extract did not produce any significant dose-related change of hematological parameters and did not show any significant toxic effects (Priya *et al*., 2010). A subchronic toxicity of the hydroethanolic mangosteen pericarp at the doses of 400, 600, and 1,200 mg/kgBW showed no effect on behavior, food, and water intake, growth, or health status in animal models (Hutadilok-Towatana *et al*., 2010).

Chivapat *et al*. (2011) reported the chronic toxicity of the ethanolic pericarp extract of mangosteen at the doses of 10, 100, 500, and 1,000 mg/kgBW. They did not show any pharmacotoxic signs and abnormalities in the hematological parameters. However, this extract at a dose of 500 mg/kgBW onward affected the body weight and increased in ALT, BUN, and creatinine. On the other hand, the seed oil of mangosteen fruit showed no lesion in the heart, liver, and spleen for 8 weeks. However, histopathology of the kidney had some pathology degrees such as diffuse glomerular and tubular degeneration (Ajayi *et al*., 2007).

CONCLUSION

The underutilized part of mangosteen fruit has potency as medicinal usage for preventing and curating metabolic diseases including obesity and lipid metabolism disorder, high blood pressure, diabetes and its complication, and cancer. Xanthone derivatives are phytochemical compounds which control a broad range of pharmacological activities. The toxicity studies showed that the use of the underutilized part of mangosteen is safe. This review supports the future clinical use of underutilized part of the fruit as a food supplement, particularly intended for metabolic disorders.

AUTHORS' CONTRIBUTIONS

Fitriana Hayyu Arifah conceived and designed the concept, collected and analyzed the data, performed the analysis, and wrote the paper. Abdul Rohman contributed to editing the manuscript, critical interpretation, and scientific guidance throughout the development of the paper. Both authors read and approved the final version.

FUNDING

This study was supported by the research grant Program of Riset Kolaborasi Indonesia (RKI), Directorate of Research, Universitas Gadjah Mada, Indonesia, with contract number 823/UN1/DIRLIT/DIT-LIT/PT/2020.

REFERENCES

Abdallah HM, El-Bassossy HM, Mohamed GA, El-halawany AM, Alshali KZ, Banjar ZM. Phenolics from *G. mangostana* alleviate exaggerated vasocontriction in metabolic syndrome through direct vasodilatation and nitric oxide generation. BMC Compl Altern Med, 2016; 16:1–10.

Adiputro DL, Widodo MA, Romdoni R, Sargowo D. Extract of mangosteen increases high density lipoprotein levels in rats fed high lipid. Univ Med, 2013; 32:37–43.

Aisha AFA, Abu-Salah KM, Ismail Z, Majid AMSA. *In vitro* and *in vivo* anti-colon canceer effects of *Garcinia mangostana* xanthones extract. BMC Compl Altern Med, 2012; 12:1–10.

Ajayi IA, Oderinde RA, Ogunkoya BO, Egunyomi A, Taiwo VO. Chemical analysis and preliminary toxicological evaluation of *Garcinia mangostana* seeds and seed oil. Food Chem, 2007; 101:999–1004.

Akao Y, Nakagawa Y, Iinuma M, Nozawa Y. Anti-cancer effects of xanthones from pericarps of mangosteen. Int J Mol Sci, 2008; 9:355–70.

Ansori ANM, Susilo RJK, Hayaza S, Winarni D, Husen SA. Renoprotection by *Garcinia mangostana* L. pericarp exctract in streptozotocin-induced diabetic mice. Iraqi J Vet Sci, 2019; 33:13–9.

Asai F, Iinuma M, Tanaka T, Tosa H. A xanthone from pericarps of *Garcinia mangostana*. Phytochem, 1995; 39:943–4.

Balasubramanian K, Rajagopalan K. Novel xanthones from *Garcinia mangostana*, structures of BR-xanthone-A and BR-xanthone-B. *Phytochem,* 1988; 27:1552–4.

Balunas MJ, Su B, Brueggemeier RW, Kinghorn AD. Xanthones from the botanical dietary supplement mangosteen (*Garcinia mangostana*) with aromatase inhibitory activity. J Nat Product, 2008; 71:1161–6.

Bigliardi B, Galati F. Innovation trends in the food industry: The case of functional foods. Trends Food Sci Technol, 2013; 31:118–29.

Boonprom P, Boonla O, Chayaburakul K, Welbat JU, Pannangpetch P, Kukongviriyapan U, Kukongviriyapan V, Pakdeechote P, Prachaney P. *Garcinia mangostana* pericarp extract protects against oxidative stress and cardiovascular remodeling via suppression of $p47^{phox}$ and iNOS in nitric oxide deficient rats. Annals Anat, 2017; 212:27–36.

Bumrungpert A, Kalpravidh RW, Chitchumroonchokchai C, Chuang C, West T, Kennedy A, McIntosh M. Xanthones from mangosteem prevent lipopolysaccharide-mediated inflammation and insulin resistance in primary cultures of human adipocytes. J Nutr Nutrit Immun, 2009; 139:1185–91.

Cencic A, Chingwaru W. The role of functional foods, nutraceuticals, and food supplements in intestinal health. Nutrients, 2010; 2:611–25.

Chae H, Kim E, Han L, Kim N, Lam B, Palk JH, Yoon KD, Choi YH, Chin Y. Xanthones with pancreatic lipase inhibitory activity from the pericarps of *Garcinia mangostana* L. (Guttiferae). Eur J Lipid Sci Technol, 2016a; 118:1–6.

Chae H, Kim Y, Bae J, Sorchhann S, Yim S, Han L, Paik JH, Choi YH, Chin Y. J Med Food, 2016b; 19:148–54.

Chairungsrilerd N, Furukawa K, Tadano T, Kisara K, Ohizumi Y. Effect of gamma-mangostin through the inhibition of 5-hydroxy-tryptamine2A receptors in 5-fluoro-alphamethyltryptamine-induced head-twitch responses of mice. B J Pharmacol, 1998b; 123:855–62.

Chairungsrilerd N, Furukawa KI, Ohta T, Nozoe S, Ohizumi Y. Gamma-mangostin, a novel type of 5-hydroxytryptamine 2A receptor antagonist. Naunyn Schmiedebergs Arch Pharmacol*,* 1998a; 357:25–31.

Chang H, Yang L. Gamma-mangostin, a micronutrient of mangosteen fruit, induces apoptosis in human colon cancer cells. Molecules, 2012; 17:8010–21.

Chang H, Huang W, Chen H, Yang L. Apoptotic effects of γ-mangostin from the fruit hull of *Garcinia mangostana* on human malignant glioma cells. Molecules*,* 2010; 15:8953–66.

Chen G, Li Y, Wang W, Deng L. Bioactivity and pharmacological properties of α-mangostin from the mangosteen fruit: a review. Expert Opinion Ther Patents, 2018; 28(5):415–27.

Chin Y, Kinghorn AD. Structural characterization, biological effects, and synthetic studies on xanthones from mangosteen (*Garcinia mangostana*), a popular botanical dietary supplement. Mini-Reviews Org Chem, 2008; 5:355–64.

Chivapati S, Chabalittumrong P, Wongsinkongman P, Phisalpong C, Rungsipipat A. Chronic toxicity study of *Garcinia mangostana* Linn. pericarp extract. Thai J Vet Med, 2011; 41:45–53.

Chomnawang MT, Surassmo S, Nukoolkarn VS, Gritsanapan W. Effect of Garcinia mangostana on inflammation caused by Propionibacterium acnes. Fitoterapia, 2007; 78(6):401–8

Dell'agli M, Di Lorenzo C, Badea M, Sangiovanni E, Dima L, Bosisio E, Restani P. Plant food supplements with anti-inflammatory properties: a systematic review (I). Crit Rev Food Sci Nutr, 2013; 4:403–13.

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. *Pharmacotherapy: a Pathophysiologic Approach*. 7th ed. Mc Graw Hill Medical, New York, NY, 2008.

Doi H, Shibata M, Shibata E, Morimoto J, Akao Y, Iinuma M, Tanigawa N, Otsuki Y. Panaxanthone isolated from pericarp of *Garcinia mangostana* L. suppresses tumor growth and metastatis of a mouse model of mammary cancer. Anticancer Res, 2009; 29:2485–96.

Farnsworth RN, Bunyapraphatsara N. *Garcinia mangostana* Linn. In *Thai Medicinal Plants*.Prachachon Co., Ltd., Bangkok, Thailand, pp 160–2, 1992.

Glasheen WP, Renda A, Dong Y, Diabetes complications severity index (DCSI)-update and ICD-10 translation. J Diabetes Complications, 2017; 31:1007–13.

Gopalakrishnan G, Balaganesan B. Two novel xanthones from *Garcinia mangostana*. Fitoterapia, 2000; 71:607–9.

Gopalakrishnan G, Banumathi B, Suresh G. Evaluation of the antifungal activity of natural xanthones from the fruits of *Garcinia mangostana* and their synthetic derivatives. J Natural Products, 1997; 60:519–24.

Gutierrez-Orozco F, Failla ML. Biological activities and bioavailability of mangosteen xanthones: a critical review of the current evidence. Nutrients, 2013; 5(8):3163–83. doi:10.3390/nu5083163

Hafeez BB, Mustafa A, Fischer JW, Singh A, Zhong W, Shekhani MO, Meske L, Havighurst T, Kim K, Verma AK. α-Mangostin: a dietary antioxidant derived from the pericarp of *Garcinia mangostana* L. inhibits pancreatic tumor growth in xenograft mouse model. Antioxidants Redox Sign, 2014; 21;doi;10.1089/ars.2013.5212.

Harrison NLJ. Xanthones from the heartwood of *Garcinia mangostana*. Phytochemistry, 2002; 60:541–8.

Huang YL, Chen CC, Chen YJ, Huang RL, Shieh BJ. Three xanthones and a benzophenone from *Garcinia mangostana*. J Nat Prod, 2001; 64:903–6.

Husen SA, Winarni D, Khaleyla F, Kalqutny SH, Ansori ANM. Activity assay of mangosteen (*Garcinia mangostana* L.) pericarp extract for decreasinf fasting blood cholesterol level and lipid peroxidation in type-2 diabetic mice. AIP Conf Proc, 2017; 1888:020026; doi:10.1063/1.5004303.

Hutadilok-Towatana N, Reanmongkol W, Wattanapiromsakul C, Bunkrongcheap R. Acute and subchronic toxicity evaluation of the hydroethanolic extract of mangosteen pericarp. J Med Plants Res, 2010; 4:969–74.

Ibrahim SRM, Mohamed GA, Elfaky MA, Zayed MF, El-Kholy AA, Abdelmageed OH, Ross SA. Mangostanaxanthone VII, a new cytotoxic xanthone from *Garcinia mangostana*. Z. Naturforsch, 2017; 73:185–9; doi:10.1515/znc-2017-0122

Ighodaro OM. Molecualr pathways associated with oxidative stress in diabetes mellitus. Biomed Pharmacother, 2018; 108:656–62.

Iinuma M, Tosa H, Tanaka T, Asai F, Kobayashi Y, Shimano R, Miyauchi K. Antibacterial activity of xanthones from guttiferaeous plants against methicillin-resistant Staphylococcus aureus. J Pharm Pharmacol, 1996; 48:861–5.

Jung HA, Su BN, Keller WJ, Mehta RG, Kinghorn D. Antioxidant xanthones from pericarp of *Garcinia mangostana* (Mangosteen). J Agric Food Chem, 2006; 54:2077–82.

Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract, 2014; 2014:943162.

Ketut AI, Salem AA, Yulinah IE, Fisheri KN. Pancreatic lipase and α-amylase inhibitory potential of mangosteen (*Garcinia mangostana* Linn.) pericarp extract. Int J Med Res Health Sci, 2016; 5:23–8.

Kurniawati M, Mahdi C, Aulanni'am A. The effect of juice mangosteen rind (*Garcinia mangostana* L.) to blood sugar levels and histological of pancreatic rats with the induction of strepzotocin. J Pure Appl Chem Res, 2014; 3:1–6.

Kusmayadi A, Bachtiar KR, Prayitno CH. The effects of mangosteen peel (*Garcinia mangostana* L.) and Turmeric (*Curcuma domestica* Val) flour dietary supplementation on the growth performance, lipid profile, and abdominal fat content in Cihateup ducks. Vet World, 2019; 12(3):402–8. doi:10.14202/vetworld.2019.402-408

Li G, Petiwala SM, Nonn L, Johnson JJ. Inhibition of CHOP accentuates the apoptotic effect of α-mangostin from the mangosteen fruit (*Garcinia mangostana*) in 22Rv1 prostate cancer cells. Biochem Biophys Res Comm, 2014; 453:75-80.

Li G, Thomas S, Johnson JJ. Polyphenols from the mangosteen (*Garcinia mangostana*) fruit for breast and prostate cancer. Frontiers Pharmacol, 2013; 4:1–4.

Lim TK. *Edible medicinal and non-medicinal plants*. vol 2. Springer, New York,pp 815–48, 2012.

Liu Q, Wang Y, Lin L. New insights in the anti-obese activity of xanthones from *Garcinia mangostana.* Food Funct, 2014; 5:1–35.

Loo AEK, Huang D. Assay-guided fractination study of α-amylase inhibitors from *Garcinia mangostana* pericarp. J Agric Food Chem, 2007; 55:9805–10.

Lusiana D, Meilinah H, Maesaroh M, Nurul F, Wahyu W. Ex vivo study of *Garcinia mangostana* L. (Mangosteen) peel extract and xanthones as anti-adipogenesis in HepG2 cell model. Int J Med Res Health Sci, 2015; 4:23–8.

Mahabusarakam W, Wiriyachtra P, Taylor W. Chemical constituents of *Garcinia mangostana*. J Natural Products, 1987; 50:474–8.

Maleki V, Jafari-Vagyghan H, Saleh-Ghadimi S, Adibian M, Kheirouri S, Alizadeh M. Effect of royal jelly on metabolic variables in diabetes mellitus: a systematic review. Complement Ther Med, 2019; 43:20–7.

Matsumoto K, Akao Y, Kobayashi E, Ohguchi K, Ito T, Iinuma M, Nozawa Y. Induction of apoptosis by xanthones from mangosteen in human leukemia cell lines. J Nat Prod, 2003; 66:1124–7.

Mishra S, Kumar MS, Stanley RC, Anal AK. Modulation of digestive enzymes and lipoprotein metabolism by alpha mangosteen extracted from mangosteen (*Garcinia mangostana*) fruit peels. J Microb Biotechnol Food Sci, 2016; 6:717–21.

Mohamed GA, Al-Abd AM, El-halawany AM, Abdallah HM, Ibrahim SRM. New xanthones and cytotoxic constituents from *Garcinia mangostana* fruit hulls against human hepatocellular, breast, and colorectal cancer cell lines. J Ethnopharmacol, 2017; 198:302–12.

Moongkarndi P, Kosem N, Kaslungka S, Luanratana O, Pongpan N, Neungton N. Antiproliferation, antioxidation, and induction of apoptosis by *Garcinia mangostana* (mangosteen) on SKBR3 human breast cancer cell line. J Ethnopharmacol, 2004; 90:161–6.

Nelli GB, Solomom A, Kilari EK. Antidiabetic effect of α-mamgostin and its protective role in sexual dysfunction of streptozotocin induced diabetic male rats. Syst Biol Reproduct Med, 2013; 1–10.

Obolskiy D, Pischel I, Siriwatanametanon N, Heinrich M. *Garcinia mangostana* L.: a phytochemical and pharmacological review. Phytother Res, 2009; 23:1047–65.

Ovalle-Magallanes B, Eugenio-Perez D, Pedraza-Chaverri J. Medicinal properties of mangosteen (*Garcinia mangostana* L.): a comprehensive update. Food Chem Toxicol, 2017; 109:102–22.

Pedraza-Chaverri J, Cárdenas-Rodríguez N, Orozco-Ibarra M, Pérez-Rojas JM. Medicinal properties of mangosteen (*Garcinia mangostana*). Food Chem Toxicol, 2008; 46:3227–39.

Peres V, Nagem TJ, Faustino de Oliveira F. Tetraoxygenated naturally occurring xantones. Phytochem, 2000; 55:683–710.

Plant List., 2013. *Garcinia mangostana* L. Available via www.theplantlist.org/tpl1.1/record/kew-2816978/ (accessed 30 August 2019).

Priya V, Jainu M, Mohan SK, Karthik B, Saraswathi P, Gopan CS. Toxicity study of *Garcinia mangostana* Linn. pericarp extract in rats. Asian J Exp Biol Sci, 2010; 1:633–7.

Redinger RN. The pathophysiology of obesity and its clinical manifestations. Gastroenterol Hepatol, 2007; 3:856–63.

Rohman A, Rafi M, Alam G, Muchtaridi M, Windarsih A. Chemical composition and antioxidant studies of underutilized part of mangosteen (Garcinia mangostana L.) fruit. J Appl Pharm Sci, 2019; 9(8):47–52.

Romeo GR, Lee J, Shoelson SE. Metabolic syndrome, insulin resistance, and roles of inflammation—Mechanisms and therapeutic targets. Arterioscler Thromb Vasc Biol, 2012; 32:1771–6; doi: 10.1161/ATVBAHA.111.241869

Ryu HW, Curtis-Long MJ, Jung S, Jin YM, Cho JK, Ryu YB, Lee WS, Park KH. Xanthones with neuraminidase inhibitory activity from the seedcases of *Garcinia mangostana*. Bioorg Med Chem, 2010; 18:6258–64.

Saklayen MG. The global epidemic of the metabolic syndrome. Current Hypert Reports, 2018; 20:1–8.

Sen AK, Uusvuori R, Hase TA, Banerji N, Sarkar KK, Mazumder PC. The structures of garcinones A, B and C: three new xanthones from *Garcinia mangostana*. Phytochemistry, 1982; 21:1747–50.

Sen AK, Uusvuori R, Hase TA, Benerji N, Sarkar KK, Mazumder PC. A xanthone from *Garcinia mangostana*. Phytochemistry, 1980; 19:2223–5.

Shibata M, Iinuma M, Morimoto J, Kurose H, Akamatsu K, Okuno Y, Akao Y, Otsuki Y. α-Mangostin extracted from the pericarp of the mangosteen (*Garcinia mangostana* Linn) reduces tumor growth and lymph node metastatis in an immunocompetent xenograft model of metastatic mammary cancer carrying a p53 mutation. BMC Med, 2011; 9:1–18.

Siró I, Kápolna E, Kápolna B, Lugasi A. Functional food. Product development, marketing and consumer acceptance—a review. Appetite, 2008; 51:456–67.

Slivnick J, Lampert BC. Hypertension and heart failure. Heart Failure Clin, 2019; 10:233–42.

Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic review of metabolic syndrome biomarkers: A panel for early detection, management, and risk stratification in the West Virginian population. Int J Med Sci, 2016; 13:25–38.

Suksamrarn S, Komutiban O, Ratananukul P, Chimnoi N, Lartpornmatulee N, Suksamrarn A. Cytotoxic prenylated xanthones from the young fruit of *Garcinia mangostana*. Chem Pharm Bull, 2006; 54:301–5.

Suksamrarn S, Suwannapoch N, Ratananukul P, Aroonlerk N, Suksamrarn A. Xanthones from the green fruit hulls of Garcinia mangostana. American Chemical Society and American Society of Pharmacognosy. 2002; 65(5):761–3.

Taher M, Zakaria TMFS, Susanti D, Zakaria ZA. Hypoglycaemic activity of ethanolic extract of *Garcinia mangostana* Linn. in normoglycaemic and strepzotocin-induced diabetic rats. BMC Compl Altern Med, 2016; 16:1–12.

Tran TH, Huyen TL, Tran TM, Nguyen TA, Pham TB, Tien DN. A new mefastigmane sulphoglycoside and polyphenolic constituents from pericarps of *Garcinia mangostana.* Nat Prod Res, 2016; 7:1–7.

Vieira LM, Kijjo A. Naturally-occurring xanthones: recent developments. Curr Med Chem, 2005; 12:2413–46.

Wang JJ, Sanderson BJS, Zhang W. Cytotoxic effect of xanthones from pericarp of the tropical fruit mangosteen (*Garcinia mangostana* Linn.) on human melanoma cells. Food Chem Toxicol, 2011; 49:2385–91.

Wang JJ, Shi QH, Zhang W, Sanderson BJS. Anti-skin cancer properties of phenolic-rich extract from the pericarp of mangosteen (*Garcinia mangostana* Linn.). Food Chem Toxicol, 2012; 50:3004–13.

Wang MH, Zhang KJ, Gu QL, Bi XL, Wang JX. Pharmacology of mangostins and their derivatives: a comprehensive review. Chin J Nat Med, 2017; 15(2):81–93. doi: 10.1016/S1875-5364(17)30024-9.

Watanabe M, Gangitano E, Francomano D, Addessi E, Toscano R, Costantini D, Tuccinardi D, Mariani S, Basciani S, Spera G, Gnessi L, Lubrano C. Mangosteen extract shows a potent insulin sensitizing effect in obese female patients: a prospective randomized controlled pilot study. Nutrients, 2018; 10(5):586; doi:10.3390/nu10050586

Watanapokasin R, Jarinthanan F, Nakamura Y, Sawasjirakij N, Jaratrungtawee A, Suksamram. Effects of α-mangostin on apoptosis induction of human colon cancer. World J Gastroenterol, 2011; 17:2086–95.

Xu Z, Huang L, Chen X, Zhu X, Qian X, Feng G, Lan W, Li H. Cytotoxic prenylated xanthones from the pericarps of *Garcinia mangostana*. Molecules, 2014; 19:1820–7.

Yeung S, Soliternik J, Mazzola N. Nutritional supplements for the prevention of diabetes mellitus and its complications. J Nutr Interm Metabolism, 2018; 14:16–21.

Yu L, Zhao M, Bai W. Immunomodulatory and anticancer activities of https://doi.org/phenolics from *Garcinia mangostana* fruit pericarp. Food Chem, 2009; 116:960–73.

Yu L, Zhao M, Yang B, Zhao Q, Jiang Y. Phenolics from hull of *Garcinia mangostana* fruit and their antioxidant activities. Food Chem, 2007; 104:176–81.

How to cite this article:
Rohman A, Arifah FH, Irnawati, Alam G, Muchtaridi, Rafi M. A review on phytochemical constituents, role on metabolic diseases, and toxicological assessments of underutilized part of *Garcinia mangostana* L. fruit. J Appl Pharm Sci, 2020; 10(07):127–146.