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Gac (*Momordica cochinchinensis* Spreng.) fruit and its potentiality and superiority in – health benefits

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Objective This review aimed to collect and summarise the scientific literature on the nutritional content, biological activities and *nutraceutical* value of *Gac fruit*.
Method we searched PubMed, Science Direct, Google Scholar, BioMed for all the studies published from 2003 to 2018 which related to the Gac fruit. However, the literature on its biological activity against disease-causing cell damage such as diabetes, obesity, and cancer were found to be limited.
Results The diversity of bioactive compounds underlies the potential use and application of medicinal plants as an excellent source of dietary supplements. Fruits that are found to be rich in multi-phytochemicals are seriously being considered as 'super' fruits due to their unique antioxidants. Gac fruit (Momordica cochinchinensis Spreng), is one of those 'super' fruits found to be rich in phytonutrients because all its fractions (i.e. aril, seeds, pulp and peel) have been widely used in folk healing and ancestral medicine. But, the entire potentiality towards the health benefits of Gac fruit is not well known or understood. Importantly, Gac fruit contains significantly higher amounts of lycopene and relatively high levels of β-carotene.
Conclusion The findings from this review suggest that the phytochemicals found in Gac fruit especially carotenoids and their potential health benefits make it an ideal candidate for the research of hyperglycemia-related eye disorders.
Keywords Gac fruit, phytochemicals, nutritional content, carotenoids, medicinal plants, phytomedicine.

Introduction

The moist tropical weather in the Southeast Asian Region (SAR) is a rich source of nutrient for medicinal plants that has been used for generations for multiple purposes and applications. From among the abundance and wide variety of fruits and vegetables found across the region, particularly in Vietnam, Gac fruit is reputed to be an exceptional source of phytochemicals.[1] "Gac" is the popular name given to this tropical fruit found in Vietnam as mentioned, as well as grown in other locations throughout the Southeast Asia Region.[2] The Gac fruit is known by several other names such as (Fak Kao) in Thailand, (Teruah) in Malaysia, (Mak Kao) in Laos, (Bhat Kerala) in India, (Moc Niet Tu) in China, and the English name is 'Spiny bitter gourd' or 'Sweet gourd'.[3]

Nutritionally, Gac fruit contains extraordinarily elevated or high-levels of carotenoids, particularly β-Carotene, lycopene, and lutein, α-tocopherol, and essential fatty acids available in its portions (i.e. peel, pulp, aril, and seeds).[4] This fruit also contains relatively high levels of polyphenols and flavonoids.[5] The biological activities of these bioactive compounds have been established via their ability to scavenge free radicals and act as antioxidants. Recently, the food and pharmacological industry have taken a keen interest in Gac fruit and producing Gac fruit products such as Gac powder, Gac oil capsules, Gac juice, and frozen Gac fruit. Moreover, these products have been released into the market serving as food additives, in cosmetics, and for medicinal and pharmaceutical purposes.[3] Figure 1 shows the morphology of Gac fruit.

Methodology

An Internet online literature search was carried out to collect and compile relevant research data for this review. The following terms were used in performing the searches; *Momordica cochinchinensis* Spreng, Gac fruit, carotenoids, age-related macular degeneration, diabetic retinopathy. All data related to Gac fruit and other keywords were downloaded via several Internet search engines: PubMed, ScienceDirect, Google Scholar, and BioMed.

Carotenoids in Gac Fruit

All parts or portions of the Gac fruit (i.e. the peel, pulp, and aril) were found to be an excellent source of carotenoids. Indeed, the aril of the Gac fruit was reported to comprise a high amount of lycopene, about 10-fold higher than that known to be in lycopene-rich fruit and vegetables.[6] In a separate study, Vuong et al.[7] reported the lycopene and β-Carotene concentrations of the edible portion of Gac fruit to be 802 and 175 μg/g respectively. Also, in the same year, Aoki et al.[6] reported 380 μg/g of lycopene and 101 μg/g of β-Carotene in Gac aril. In a further study, Ishida et al.[1] found very high levels of carotenoids (β-Carotene, α-carotene, and lycopene) in Gac aril, with concentrations of 718, 107, and 2227 μg/g, respectively. Another study reported Gac aril content of lycopene and β-Carotene was 408 and 83 μg/g respectively.[8] While Nhung et al.[9] mentioned that Gac fruit had the highest amount of lycopene with a concentration of 3728 μg/g FW and that the concentration of β-Carotene was

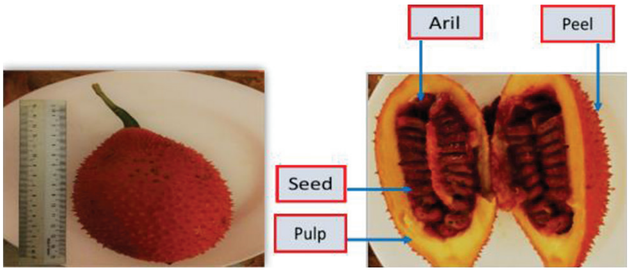

Fig. 1 **Gac (*M. cochinchinensis* Spreng) fruit morphology.**

similarly very high at 379 μg/g FW. Recent reports have indicated very promising and excitingly high-levels of both lycopene and β-Carotene in Gac aril, of 6800 and 2900 μg/g respectively.[10] A further study reported concentrations of 6300 and 5700 μg/g for lycopene and β-Carotene respectively.[11] Investigating the carotenoids in Gac fruit, carrot root and tomato fruit, as to which was more digestible, determined that both carotenoids (lycopene and β-Carotene) from Gac fruit were found to be at least eight times higher than the carotenoids found in carrot root and tomato fruit.[12]

Besides Gac aril, the yellow pulp and the peel of the Gac fruit were equally found to be a rich source of carotenoids. It was reported that the total carotenoid content of Gac pulp was 283 μg/g, and this concentration is high compared with other carotenoid-rich fruits.[8] The Gac pulp content of carotenoids was further analysed, revealing that Gac pulp contains 22 μg/g of β-Carotene and 0.9 μg/g of lycopene, and in addition to β-Carotene, the Gac pulp was also found to contain zeaxanthin and β-Cryptoxanthin.[6] Furthermore, in addition to lycopene and β-Carotene, Gac peel was found to be remarkably, if not extremely rich in lutein, and much higher than found in the other fractions of the fruit, (52,020 μg/g).[5] However, at this stage, only the aril has been processed as the peel and pulp which constitute a significant quantity (15% and 42% respectively) of the total weight of the fruit, are usually discarded.[3] Previous *in vitro* digestion studies concluded that the bioavailability and bioaccessibility of carotenoids from Gac fruit aril were much higher than those from carrot and tomato.[12]

Fatty Acids in Gac Fruit

In addition to carotenoids, the fatty acid content found in Gac fruit has been investigated by several researchers. Fortunately, the existence of unsaturated fatty acids in Gac fruit was found to be relatively high.[1] It was reported that 100 g of Gac seed pulp contains 852 mg of fatty acids, and of that total amount, 70% was found to be unsaturated and 50% was polyunsaturated.[13] A further investigation reported that the Gac seed pulp content of fatty acids was 102 mg/g of the edible portion.[7] Remarkably, oleic, palmitic, and linoleic acids were found to be predominant in Gac aril (32.3%, 29.2%, and 28.1% respectively), while the predominant fatty acid found in Gac seed was stearic acid with small levels of linoleic, oleic and palmitic acids of 60.5%, 20.3%, 9%, and 5.6% respectively.[1] In a separate study by Newly, the total percentage of unsaturated fatty acids in Gac aril was reported to be 71.38%, which was much higher than that of saturated fatty acids, with a final percentage of 28.62%. Indeed, the most dominant fatty acids were oleic acid 48.99% followed by palmitic acid 24.18% and linoleic acid 21.09%.[14]

Phenolic and Flavonoid Compounds in Gac Fruit

Phenolic and flavonoid compounds were also found in Gac fruit. A study reported that the concentrations of phenolics and flavonoids found in Gac fruit were about 26.08 and 1.32 mg/100 g, respectively.[15] Another study reported that the Gac fruit content of phenolics and flavonoids was investigated by several researchers, where it was determined that Gac peel, pulp, and aril content of phenolics was 55, 205, and 191 μg/g FW respectively, whereas Gac peel, pulp, and aril content of flavonoids was 0.118, 0.143, and 0.084 mg/g FW respectively.[16] Gac fruit content of the phenolic and flavonoid compound variety among the fractions based on the maturity stages determined that ferulic acid and *p*-hydroxybenzoic acid were most apparent in Gac pulp, while apigenin, rutin, and luteolin were the main compounds found in mature pulp and aril.[5]

Traditional and Epidemiological Uses

Gac fruit is indigenous to Vietnam and Southeast Asian countries and is used and consumed as a dietary supplement as well as for medicinal purposes. In Vietnam, Gac aril is cooked with rice to provide a scrumptious glossy look, with an oily taste for the slimy traditional rice dish named as ("xoi" gac), which is served during special occasions and festivals like Lunar New Year, birthdays, and weddings.[3] Besides that, Gac oil after being extracted from the aril has also been used as a tonic and given to lactating or pregnant women and children to treat dry eyes (xerophthalmia) and night-blindness vision.[2] It is also reported that the application of Gac oil is used to heal skin infections, wounds and burns, and has helped to stimulate cell growth and closure in wounds.[2]

In China, the seed of the Gac fruit has been utilised for many generations. The Gac seed (in Mubiezi, China) has been traditionally used to treat inflammation, swelling, scrofula, tinea, diarrhoea with skin infections such as sores, carbuncles, furuncles and boils in humans and animals.[17] In Bangladesh, the *M. cochinchinensis* Spreng known as 'Kakroal' or 'kark gach', uses all Kakroal fractions (i.e. fruit, seed, leaf, and roots) in medicinal systems for the treatment of various ailments such as cancer, diabetes, liver diseases, skin infections, itches, rheumatoid arthritis, colic, and blood purification.[18] Thirty days of Gac fruit nourishment was found to improve β-Carotene levels among 185 preschoolers who were selected based on their high risk of Vitamin A deficiency.[7]

Antioxidant Activities of Gac Fruit

The antioxidant activity of Gac fruit has been examined using diphenyl-picrylhydrazyl (DPPH) radical scavenging, ferric reducing antioxidant power (FRAP), and 2,2'-azino-bis(3-ethy lbenzothiazoline-6-sulphonic acid (ABTS). These assays are widely used and accepted in evaluating the antioxidant properties of different compounds in foods, plants, fruits, and herbs. Moreover, different fractions of the Gac fruit at different maturity stages have been assessed regarding their potential antioxidant FRAP, by applying DPPH assays. The results showed that Gac aril at the fully ripened stage had the highest FRAP value at 531.17 μmol/g. In the same study, the DPPH assay test showed that Gac peel and pulp had the highest antioxidant activity at the immature stages of 2.56 and 2.35 μmol/g, respectively.[5] A separate study reported that DPPH and FRAP assessments of 100 g of Gac fruit extract, were equivalent to 45.1 and 5.8 mg, respectively.[15] Moreover, Gac peel extract using ethyl acetate showed the ABTS antioxidant capacity yield of 737 μM trolox equivalent (TE) /100 g dry weight (DW) with total carotenoids of 271.1 mg/100 g DW.[19] The seed of the fruit has also been found to be rich in chymotrypsin inhibitor.[20] The antioxidant activities of a chymotrypsin inhibitor from Gac seed have been established in rat hepatocyte culture exposed to *tert*-butyl hydroperoxide (*t*-BHP)-induced oxidative stress.[21]

Anticancer Activity of Gac Fruit

Several studies investigated the ability of Gac fruit extract to inhibit and suppress the proliferation of several cancer cell lines via various mechanisms. A crude water extract obtained from the Gac fruit was assessed to determine its antitumor and Anti-angiogenic activities *in vitro* and *in vivo,* which resulted in the cell proliferation of two cancer cell lines (colon 26-20 and HepG2 cells) significantly inhibited when treated with the water extract. Indeed, the crude water extract was able to suppress the progression of cancer by reducing the wet tumour weight by 23.6% in a 'rat' cancer group. Moreover, histology and immunohistochemistry investigations appeared significant toward decreasing vascularisation for the Gac treated group.[22] It was also reported that a water extract taken from Gac aril significantly reduced the cell viability of two cancer cell lines, notably MCF-7 breast cancer and melanoma with a rate of 60% and 71%, respectively.[11] Notwithstanding, Gac aril extract has shown an anticancer effect against the human MCF-7 breast cancer cell line by both apoptosis pathways (intrinsic and extrinsic). The mixture of hexane, acetone, and ethanol was successfully used to extract carotenoids from Gac aril that were then compared with lycopene and tamoxifen. Cell shrinkage and chromatin condensation have also been induced by aril extract using 4',6-diamidino-2-phenylindole (DAPI) fluorescent staining, while flow cytometry assay showed a higher percentage of MCF-7 cells in the early apoptosis stage. Moreover, aril extract was found to be capable of enhancing the activity of caspase-6, -8, and -9, where the expression of the proapoptotic BAX gene dramatically increased when assessed by Real-time polymerase chain reaction (RT-PCR).[10]

Furthermore, the anticancer potentiality of Gac seed extract was also investigated in a study which showed that Gac seed extract appeared to exhibit potent inhibitory effects against human breast cancer ZR-75-30 cells. Moreover, the extract significantly repressed the expression secretion of two matrix metalloproteinases MMP-2 and MMP-9 when assessed based on western blot and gelatin zymography tests.[23] The anticancer activity of Gac seed extract was further explored on human SGC7901 and MKN-28 gastric cancer cell lines, where the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)

assay revealed that the survival of both cell lines had significantly decreased when compared with the control. Furthermore, Gac seed extracts were able to promote apoptosis by increasing the enzyme activities of caspase-3 and -9 and via PARP and p53 signal pathways.[24] Notably, the antiproliferative activity of Gac seed extract has been established again, and the ethanolic extract of Gac seed was found to be capable of suppressing the proliferation of A549 lung cancer cells by inducing apoptosis via the activation of p53 and inactivation of PI3K/Akt signalling.[25] Recently, Gac seed extracts showed anticancer potential activity against two melanoma (MM418C1 and D24) cell lines.[26]

DNA Protective Activity of Gac Fruit

The DNA protective effect of Gac fruit against TK6 human lymphoblast cells, induced by H_2O_2 and ultraviolet UVC was investigated. In the previous study, it was found that TK6 exposure to 50 μM H_2O_2 for 5 min, produced massive oxidative DNA damage, while TK6 exposure to UVC significantly enhanced DNA migration, when the TK6 cells were treated with Gac peel extract using ethanol 95% and 50%, thus leading to a significant decrease in DNA damage.[27]

Antimicrobial Activity of Gac Fruit

Gac pulp (flesh) and seed pulp (aril) were examined concerning their potential activity against different strains of both Gram-positive and Gram-negative bacteria. The results of such work indicated that water and ethanolic extraction of Gac pulp displayed higher antibacterial effect on Gram-positive strains than Gram-negative strain bacteria. Accordingly, the highest antibacterial activity was observed in the ethanolic extract of Gac flesh against both strains, *Micrococcus luteus* 745 (20 mm) and *M. luteus* 884 (18.5 mm) inhibition zone.[28] Another study assessed the antimicrobial activities from various parts of the Gac fruit (i.e. peel, pulp, and aril) against six pathogenic bacteria (*Escherichia coli*, *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, and *Klebsiella pneumonia)*. Such results demonstrated that the data of this study confirmed that ethanolic extraction of various parts from Gac fruit had antimicrobial activity against all pathogenic strains, as mentioned previously.[29]

Antiulcer Activity of Gac Fruit

It has also been documented that 7 and 14 days of treatment with an ethanolic extract of Gac seed, significantly accelerates the healing of acetic acid via enhancing and upregulation of the angiogenesis, and increases the expression of mRNA as well as the vascular endothelial growth factor (VEGF), tested by real-time PCR and western blot.[29]

Anti-inflammatory Activity of Gac Fruit

Surprisingly, Gac seed is found to be a rich source of saponins, which are known for their health benefits.[30] Two triterpenoid saponin compounds (Gypsogenin glycoside and Quillaic acid glycoside) were isolated and examined regarding their anti-inflammatory activity. For example, compound 2 (Quillaic acid glycoside) which is a saponin compound that isolated from Gac seed demonstrated anti-inflammatory effects in RAW 264.7 cells via inhibiting the lipopolysaccharide-induced expression of nitric oxide and IL-6 via the NF-κB pathway.[31]

Other Health Benefits of Gac Fruit

Recently, two saponin compounds which were isolated from Gac seed showed a promising therapeutic effect against cisplatin-induced renal damage in LLC-PK1 kidney cells *in vitro* via blocking mitogen-activated protein kinases (MAPKs) signalling cascade.[32] Likewise, the gastroprotective effect of Momordica semen extract has also been explored *in vivo*. The pre-treatment with Momordica saponin I as an ingredient isolated from the Momordica seed decreased gastric mucosa damage, thereby reducing the progressing acute and chronic gastrointestinal disorders (e.g., gastritis and gastric ulcer).[33] The adverse reproductive parameters of male rats induced by valproic acid (VPA) was investigated. The *M. cochinchinensis* aril was mixed with distilled water, filtered, then dried and given orally to the rats in different concentrations. The protective effect of the extract against adverse male reproductive parameters and testicular damage induced by VPA was evident; the aril extract significantly protects the decrease of the weights of the epididymis and seminal vesicle. The aril extract also increased the sperm concentration and seminiferous diameter. Moreover, testicular histology tests confirmed dramatically declining testicular histopathologies as compared with the VPA group.[34] Table 1 explained the biological activities of Gac fruit parts extracts.

Further Discussion and Integration

This study aims to scientifically summarise the literature studies that have characterised the bioactive compounds in Gac fruit and its portions. However, there is limited literature presently

Table 1. **Health benefits and biological activities of Gac fruit**

Gac part	Type of study	Health benefits	Mechanism of actions
Fresh Gac aril	Clinical trial	Provitamin A activity	Improve β-carotene status which may lead to improve eye vision.[7]
Gac peel, pulp and aril	*In vitro*	DNA protective activity	Decrease DNA damage induced by H_2O_2 and UVC.[27]
Water extract of Gac aril	*In vitro* and *In vivo*	Anti-tumor and Anti-angiogenic activities	Inhibition of the growth of colon adenocarcinoma cell, reduce wet tumor, reduce the blood vessels density around the carcinoma.[22]
Gac aril	*In vitro*	Anticancer activity	Suppression of the proliferation of breast cancer (MCF7) and melanoma (MM418C1 and D24) cell lines.[11]
Gac pulp and aril	*In vitro*	Antimicrobial activity	Inhibition Gram-positive and Gram-negative bacteria growth.[28]
Peel, pulp and aril	*In vitro*	Antioxidant and antimicrobial	Scavenge radical activity and ferric reducing power, inhibition growth of different pathogenic bacteria such as (*E. coli, S. aureus*, and *B. cereus*).[16]
Gac aril	*In vitro*	Anticancer	Induce cell apoptosis of MCF-7 via intrinsic and extrinsic signalling pathways.[10]
Gac seed	*In vitro*	Anti-inflammatory activity	Reduce the production of nitric oxide (NO), decrease mRNA level of NO synthase (*i*NOS) and cyclooxygenase (COX)-2, inhibit the translocation of p65 and p50 of RAW 264.7.[35]
Gac aril	*In vivo*	Male reproductive improvement	Protected against decrease weights of epididymis and seminal vesicle, increased sperm concentration and seminiferous tubular diameters.[34]
Gac seed	*In vitro*	Anti-inflammatory	Inhibited lipopolysaccharide-induced expression of nitric oxide and IL-6 via NF-κB pathway.[31]
Gac seed	*In vivo*	Anti-gastritis and wound healing activities	Protective effect in a helicobacter pylori-insulted gastritis model, wound healing effect on cutaneous injury and stimulation of calcitonin gene-related peptide and somatostatin receptors.[33]
Gac seed	*In vitro*	Renoprotective activity	Ameliorate of cisplatin-induced nephrotoxicity effect, blocking of MAPKs signalling cascade.[32]
Gac seed	*In vivo*	Antiulcer and wound healing activities	Acceleration of gastric ulcer healing via upregulation of VEGF expression in an acetic acid rat model.[29]
Gac seed	*In vitro*	Anticancer activity	Inhibition cell survival of SGC7901 and MKN-28 gastric cancer cells, seed treatment block the cell cycle at S phase downregulation of PARP and Bel-2 proteins, activation of the enzymatic pathways caspase-3, -9 and -8.[24]
Gac seed	*In vitro*	Anticancer activity	Inhibition the A549 and H1299 lung cancer cell growth, induce apoptosis via upregulation of p53, Bax and downregulation of Bcl-2 and PI3K/Akt signal pathways.[25]
Gac seed	*In vitro*	Anticancer activity	Suppression the proliferation and inhibit the invasion and migration of the breast cancer cell line (ZR-75-30), inhibition the expression of MMP-2 and MMP-9.[23]
Gac seed	*In vitro*	Antioxidant activities	Improve hepatocytes cell damage induced by *t*-BHP, decreased lipid peroxidation and oxidized glutathione (GSSH) that induced by *t*-BHP and increased glutathione (GSH) depletion.[21]
Gac seed	*In vitro*	Antioxidants and anticancer activities	Free radical scavenging via DPPH and ABTS tests and ferric reducing power, suppression of the proliferation of human melanoma cells MM418C1 and D24 lines.[26]

available regarding the biological activity of Gac fruit to fight against and prevent disease-causing cell damage such as cancer, diabetes and its complications, obesity, inflammation, atherosclerosis, cardiovascular disease, and microbial infections. Moreover, a limited number of published papers have reported the abundance of multiple phytochemicals (e.g., carotenoids, phenolic compounds, flavonoids, vitamin E, and essential fatty acid) in Gac fruit and its portions. The richness and abundance of the Gac fruit in various bioactive compounds also make it a 'super' fruit possessing several health benefits. It is worth mentioning that the superiority of this fruit will undoubtedly attract the best researchers in this field in undertaking challenging and possibly lucrative investigations in the future.

Furthermore, most of the studies related to Gac fruit have mainly emphasised the phytochemicals and/or bioactive compound contents especially carotenoid pigments. Due to the presence and high concentrations of carotenoids, this also gives the Gac fruit it's bright, shiny, deep orange-red colour. Indeed, β-Carotene, lycopene, and lutein were the primary carotenoids that were mostly quantified.[1,5–7,9,11] Most of the previous studies investigated the Gac fruit-rich extract, with little focus on the actual compounds. Therefore, the purification of β-Carotene, lycopene, and lutein and their application separately, could be more effective and conducive to various diseases. Fortunately, carotenoids in Gac fruit are mostly combined with oil and essential fatty acids. This characteristic enhances the priority and thereby promoting the advantages in the overall process of producing Gac fruit than other fruits and vegetables. Indeed, this is mainly because of the oil aiding in the absorption and digestion of carotenoids in the gastrointestinal tract in the digestive system.[12,36]

The phytonutrients in the parts of the Gac fruit (i.e. peel, pulp, and aril) and discussed earlier in this study, have been found to be rich in carotenoids. However, from among these portions, only the aril is processed while the other parts, like the peel and pulp, are usually discarded and considered as wastage, rather than valuable carotenoids or bi-products of the fruit.[3,4] Surprisingly, the concentration of lutein is considerably high in Gac peel compared with the other parts.[5] Lutein is one of the carotenoid pigments (xanthophylls) found to be uniquely concentrated in the retina of the eye.[37] Interestingly, several studies have reported that low levels of lutein are associated with eye impairment and disorders such as diabetic retinopathy and age related-macular degradation. Prior studies have also revealed that diabetic retinopathy (DR) and age-related macular degeneration (AMD) are related to having a relatively lower level of lutein and other xanthophylls.[38,39] Therefore, Gac peel-rich lutein pigment should be utilised and processed as a significant source of lutein supplementation rather than merely being wasted and discarded.

DR and AMD are the leading cause of blindness in developing and developed countries as mentioned earlier and are characterised by chronic exposure of hyperglycaemia by the retina.[40–42] However, the present treatment of the disease has many drawbacks such as retinal haemorrhage, retinal detachments, in addition to the treatment costs which place a considerable burden on the patients and their families.[43–45] The role of carotenoid pigments in the protection and avoidance of eye disease has been well acknowledged in the literature.[46–48] Therefore, based upon the information presented and discussed in this review, and to the best of the author's knowledge, there have been no studies investigating the use of Gac fruit-rich carotenoid extracts for the treatment of eye disorders such as DR and AMD.

Many pathophysiological pathways are involved in the development and progression of DR and AMD diseases,[49] and many of which have faced speculation toward the disruption of the balance of the ocular angiogenesis process in favour of pro-angiogenic signals.[50] Despite the recent progress in understanding the pathogenesis of DR and AMD, including the role of growth factors, the diseases are still neither preventable nor curable. However, recent studies have indicated that regulating angiogenic markers may be an opportunistic target in the treatment of DR and AMD.[51] Currently, attempts have been made to utilise phytotherapy such as medical herbalism, which relies on an empirical appreciation of medicinal herbs and its nutraceuticals due to the degree of safeness, efficacy and pharmacological action in the prevention and treatment of chronic diseases.[52–55] For the later reasons, numerous efforts have been employed for screening and development of Anti-angiogenic products from natural sources. Notwithstanding, previous attempts have also been used on several phytochemicals and their derived metabolites from various medicinal plants, by testing their action and response as Anti-angiogenic agents.[48,56] The outcome of such studies was promising but far from perfect and acceptable, due to the low level of extracted carotenoids, particularly lutein in the extraction yield. As mentioned previously, Gac fruit is abundantly rich in carotenoids and contains high quantities of lutein as compared with other medicinal plants. Indeed, this advantage could enable novel, if not innovative approaches to be adapted to extract a prominent level of carotenoids from the fruit, and to examine its pharmacological effect and biological mechanisms of action. Likewise, the determination of the pharmacological function using combined and individual molecules can also lead to exploring the mechanisms of action. Discovering the mechanistic pathway by which the mechanism derives the molecules, and reverse or normalise the angiogenic process in diabetic patient's eyes would be incredibly valuable. However, to date, there have been no large-scale studies to investigate the effect of the Gac fruit's rich extract against angiogenesis markers related to eye disease among all levels including *in vitro, in vivo*, and clinical studies. Therefore, Gac fruit and its multi-content of phytochemicals and especially carotenoids could be an ideal agent for a myriad of diseases, but further research studies would still be required to investigate the efficacy, the nature and role of Gac fruit and its bioactive compounds by the combined and synergistic use. Figure 2 shows the potential future work that can be conducted using Gac fruit and its parts extracts.

herefore, considering all the information discussed, discovering new sources that would be able to regress, slowdown, or delay the progression of DR and AMD would be highly advantageous and recommended. Finally, Gac fruit-rich carotenoids may be a potential agent to control or to balance the angiogenesis process, which may open and expose new insights and knowledge for the cure and treatment of angiogenesis-related eye diseases.

Conclusion

Gac (*M. cochinchinensis* Spreng.) fruit, is a conventional fruit found in Vietnam and other Southeast Asian countries, which contains relatively high levels of carotenoids, especially lycopene and β-Carotene. The Gac fruit is a distinctive and promising phytonutrient which has been used for generations for

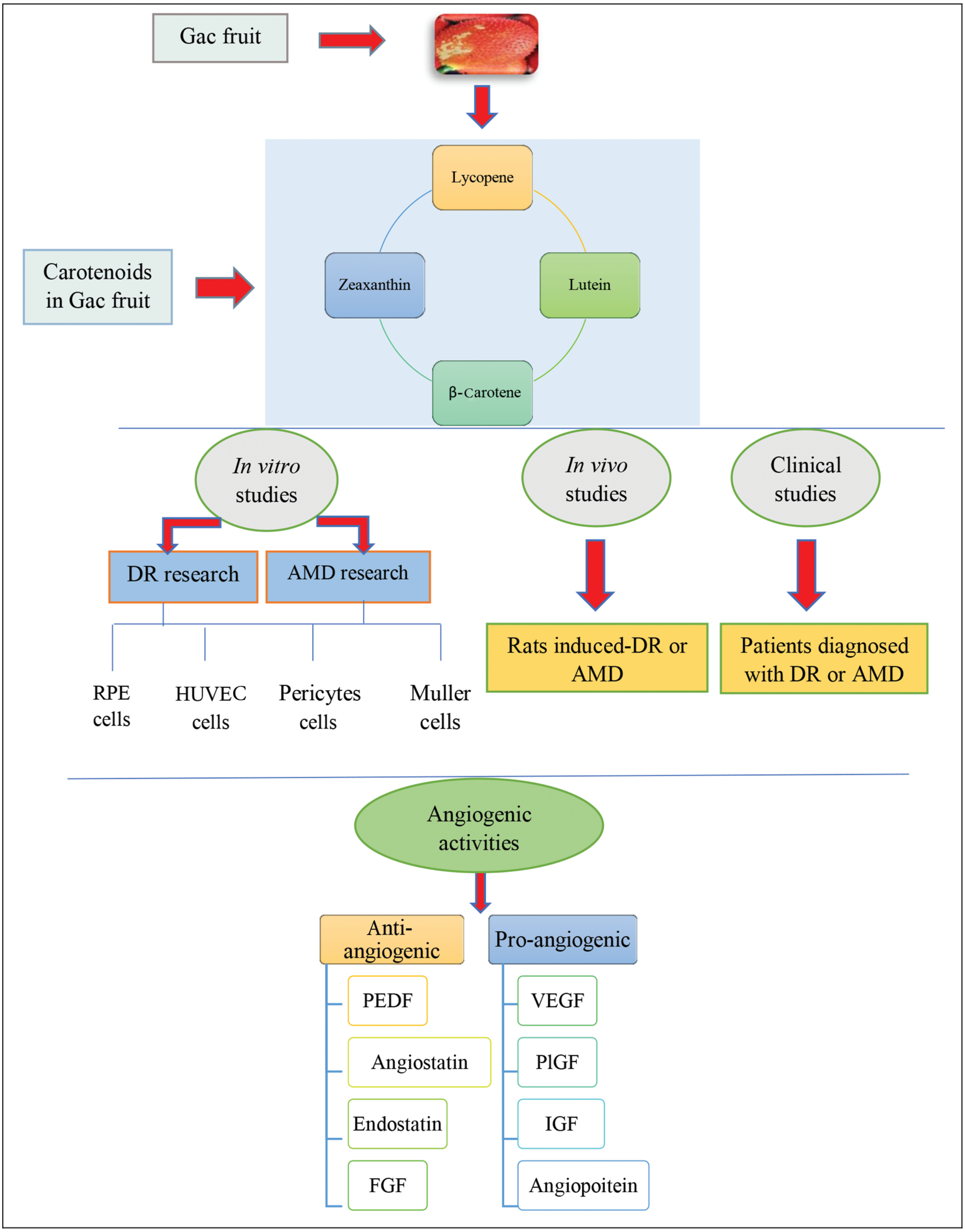

Fig. 2 **Potential future research on Gac fruit-rich carotenoids fruit. RPE, retinal pigmented epithelial cells; HUVEC, human umbilical vein endothelial cells; PEDF, pigment epithelium-derived factor; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; PlGF, placenta like growth factor; IGF, insulin-like growth factor.**

both nutritional and medicinal purposes. Additionally, used in the body, β-Carotene is converted to vitamin A, thereby enhancing the immune system, helping to prevent eye-associated diseases. Indeed, studies undertaken in recent years have exploited this conviction by revealing the high levels of antioxidants contained in the fruit. Therefore, it is not surprising to observe the current research in nutritional sciences and health now being directed with utmost enthusiasm and motivation toward this unique fruit at both the cellular and molecular levels.

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Author Contributions

AA perfumed the work and manuscript formatting; FA conceived, supervised and edited the review; AI and NE supervised, and contributed to the structure of the manuscript and review. All authors read and approved the final manuscript.

Conflict of Interest

The authors have no conflict of interest related to this manuscript.

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