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NUTRITIONAL AND PHARMACOLOGICAL PROPERTIES OF AGRO-INDUSTRIAL BY-PRODUCTS FROM COMMONLY CONSUMED FRUITS

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Research

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ABSTRACT

Presently, there is growing interest to use agricultural wastes as by-products for further exploitation as food additives or supplements. The waste product which is typically thrown into the environment has been revealed to exhibit certain nutritional and pharmacological properties. Some functional compounds have been reported to exert significant nutritional and pharmacological properties such as antioxidant, anticancer, antidiabetic, antimicrobial, etc. Based on recent literature, many reports or studies focused on the utilization and pharmacological effects of some selected agro-industrial by-products. This trend could provide the theoretical basis for further rational development and utilization of the waste for the therapeutic and health purposes.

Keywords: fruits by-products, fruits waste, nutritional value, pharmacological properties

INTRODUCTION

Fruits contain a significant number of vitamins, minerals and dietary fibre which are vital to sustaining health status of the human body. Many studies had shown that the consumption of fruits could help reduce the risk of many illnesses such as diabetes, cancer, cardiovascular diseases and other illnesses [1]. The edible part of fruits not only become a high demand in consumption but also in industrial processing. Due to that, wastes from the fruits such as peels, seeds and other parts are generated in large quantities. This becomes a critical disposal problem, as they can affect the environment and need to be properly managed and/or utilized. For the last decade, efforts have been made to improve methods and ways of recycling fruits and vegetable wastes [2].

The whole tissue of fruits is known to have bioactive compounds, such as phenolic compounds, carot-

enoids, vitamins and other essential nutrients. Besides that, fruits waste has also been reported to show some significant antioxidant activities. Interestingly, in most cases, the waste by-product has similar or even higher contents of antioxidant and antimicrobial compounds than the actual product has.[3] Due to that, there is growing interest to use the fruit wastes as the sources of bioactive compounds and use them in food, cosmetics and pharmaceutical industry [3].

The waste also consists various essential nutrients such as natural sugars, minerals, organic acid and dietary fibre [4]. Many studies had shown that this waste contains a variety of functional compounds and this has been reviewed by Schieber, Stintzing [3], Soong and Barlow [5], Balasundram, Sundram [6] and Rudra, Nishad [4]. As the fruit wastes are very rich in bioactive components, they offer selected therapeutic effects in sustaining human health [7]. Therefore, the objective of this review is to highlight the potential of selected by-products of commonly consumed fruits as a raw material for the therapeutic application.

METHOD

For the present review, information regarding nutritional, medicinal and biochemical properties of by-product derived from commonly consumed fruits were gathered via various searching engines. The scientific databases searched in this review include PubMed, Elsevier, GoogleScholar, Springer, etc. Commonly consumed fruits (orange (*Citrus*), apples (*Malus domestica*), banana (*Musa*), grape (*Vitis*), watermelon (*Citrullus lanatus*), papaya (*Carica papaya* L.), strawberries (*Fragaria ananassa*), mango (*Mangifera indica* L.) and rambutan (*Nephelium lappaceum*) were chosen based on the basis of the consumption per capita from USDA database 2013 [8] and Agrofood Statistic 2014 [9].

BY-PRODUCT USED IN PHARMACOLOGICAL STUDIES

Various health-promoting properties of by-product have been studied by using *in vivo* and *in vitro* assays.

Antibacterial properties

Rambutan

The extracts of rambutan peels had shown potential activity against many bacteria. The ether [10], methanol [10, 11], aqueous [10], petroleum ether [12], chloroform [12] and ethanol [12, 13] extracts exhibited antibacterial activity against *Staphylococcus aureus*. Besides that, the ether, methanol and aqueous extracts also showed activity against *Vibrio cholera, Enterococcus faecalis, Staphylococcus epidermidis* and *Pseudomonas aeruginosa* [10] while chloroform and ethanol extracts showed activity against *Bacillus cereus* and *Proteus vulgaricus*. Ethanol extract also exhibited activity against *Salmonelli typhi*, *Bacillus subtiis* and *Escherichia coli* [12]. The methanol extract was reported to show activity against methicillin-resistant *S. aureus* and *Streptococcus mutans* [11]. Besides the peel, the seed of rambutan also showed some potential as antibacterial. The aqueous extract of rambutan seed has shown significant antimicrobial activity against *Bacillus subtilis, Streptococcus pyogenes, S. aureus, P. aeruginosa* and *E. coli* [14].

Apple

Polyphenols in apple pomace had shown strong inhibition in bacterial activities on *E. coli* and *S. aureus* [15]. The ethanolic extract from the peel of the Apple cultivar Annurca exhibited antimicrobial activity against *Bacillus cereus* and *Escherichia coli* serotype O157:H7 [16].

Aqueous acetone extract of Red Delicious' peels shows potent effects in inhibiting bacteria growth both against Gram-positive bacteria (*S. aureus*, *Staphylococcus epidermidis* and *Bacillus cereus*) and Gram-negative bacteria (*E. coli*, *Pseudomonas aeruginosa* and a *Salmonella* spp. Strain isolated from food) and also against the yeast (*Candida albicans*) and the mould (*Aspergillus niger*) [17].

Peel of *Royal Gala* and *Granny Smith* showed an antimicrobial effect against human pathogens of *E. coli, S. aureus, P. aeruginosa, Enterococcus faecalis* and *Listeria monocytogene* [18]. However, in another report, peel of Granny Smith apple was found to be inactive in *Bacillus subtillis*, *Micrococcus sp*., *S. au-*

reus, *E. coli* and *Shigella sonnei* except against *Proteus vulgaris* [19].

Orange

An orange *(C. sinensis)* showed effective inhibition towards Gram-positive Bacteria: *B. subtillis*, *Micrococcus sp*. and *S. aureus* [19]. On the other part, essential oil of sweet orange peel can effectively inactivate *V*. *parahaemolyticus*, *S*. *typhimurium*, and *E. coli* but not *S. aureus*, on the surfaces stainless steel and plastic cutting board pieces [20].

Water and ethanol extract of the orange peels and seeds showed positive activity against *E. coli* and *S. aureus* [21]. In addition, the ethanol extract of the orange peels also exhibited activity against *P. aerginosa* [22].

Strawberry

Aqueous and methanol extracts of strawberry pomace have shown significant antibacterial activities against *Serratia marcescens, E. coli, Bacillus cereus* and *B. subtilis* [23].

Grape

The supercritical extracts obtained from Merlot grape pomace by SC-CO_2 at 300 bars at 50°C exhibited more effective activity against Gram-positive bacteria (*S. aureus* and *B. cereus*) compared to Gram-negative bacteria (*E. coli* and *Pseudomonas aeruginosa*) [24].

Tseng and Zhao [25] examined the inhibitory effect of pomace and skin extracts from two grape types (Pinot Noir and Merlot) against *L. innocua* than *E. coli*. The results showed that the pomace extract exhibited stronger antibacterial activity compared to skin extracts for both grape types. However, pomace and skin extracts from Pinot Noir showed stronger antibacterial activity compared to Merlot type. The pomace extracts from Kalecik karasi and Emir grape cultivars have antibacterial activity on *Aeromonas hydrophila, B. cereus, Enterobacter aerogenes, E. faecalis, E. coli, E. coli* O157:H7, *Mycobacterium smegmatis, Proteus vulgaris, P. aeruginosa, P. fluorescens, Salmonella enteritidis, Salmonella typhimurium*, *S. aureus* and *Yersinia enterocolitica* [26]. Pomace grape from Cabernet Sauvignon and Syrah varieties have shown potent antibacterial activities against *E. coli, S. typhi, S. aureus* and *L. monocytogenes* [27].

Grape seed extract showed strong antibacterial activities against *Bacillus cereus, Bacillus coagulan, Bacillus subtilis, S.* aureus, *E. coli, P. aeruginosa, Aeromonas hydrophila, Enterobacter aerogenes, Enterococcus faecalis, Klesiella pneumoniae, Mycobacterium segmatis, Proteus vulgaris, Pseudomonas fluorescens, Salmonella enteritidia, Salmonella typhimurium* and *Yersinia enterocoliyica* [28, 29]. Grape seed extract also showed effective antibacterial activity against *Campylobacter* spp. [30].

Banana

Aqueous extract of yellow banana peel showed significant antibacterial activity against *S. aureus, S. pyogenes*, *M. catarrhalis, E. aerogenes* and *K. pneumoniae* but no effect against *C.albicans* and *E. coli* [31]. While, ethyl acetate fraction from green banana peel showed significant antibacterial activity against *S. aureus, E. coli, B. subtilis, S. enteritidis* and *B. cereus* [32]. Ethanol extract of banana peel showed antibacterial activity against *A. niger, A. flavus, P. digitatum, F.oxysporum, C. albicana, E. coli, S. aureus* and *P. aerginosa* [22].

Watermelon

Ethanol extract of watermelon peel showed antibacterial activity against *F.oxysporum, C. albicana, E. coli, S. aureus* and *P. aerginosa* [22].

Mango

Mango seed and peel extracted in water and ethanol showed antibacterial activity against *S. aureus* and *B. subtilis* [13]. Mango seed kernel extract and oil showed antibacterial activity against *E. coli* [33]. Khammuang and Sarnthima [34] reported that sheath seed and seed kernel extract of mango from four Thai varieties (Chok-a-nan, Fah-lun, Kaew and Nam-dok-mai) have antibacterial activity against *B. cereus*, *B. subtilis*, *P. aeruginosa* and *S. typhi*. Mango seed ker-

nel also was reported to have antibacterial against *Citrobacter freundii. Enterobacter aeruginosa, E. coli, Gordonia bronchialis, Gordonia sp.,* Gram-negative *Listeria monocytogens, Mycobacterium senegalense, Mycobacterium smegmatis, Nocardia asteroids, Nocardia farcinica, Nocardia otitiscaviarum, P. aeruginosa, Rhodococcus equi, S. typhi, Shigella flenerri, S. aureus, Streptococcus pyogenes, Streptococcus sp*. and *Yersinia enterocolitica* [35].

Mango seed kernel from two varieties (Bagnapalli and Senthura) was compared for antibacterial activity against *S. aureus* and *P. aeruginosa,* and the results showed that Bagnapalli variety was more effective in antibacterial activity than the Senthura variety [36]. Another study compared the antibacterial activity of mango seed kernel from three varieties (waterlily, lemak and shakran) against *E. coli, B. subtilis, S. aureus* and *P. auruginosa* and the results showed that waterlily variety has the highest antibacterial activity [37].

Papaya

Seed and peel of papaya possessed antibacterial potential against *S. aureus, E. coli* and *P. aeruginosa*. However, the potency of the activity depends on the extraction solvent used where petroleum ether showed the highest activity, followed by 1% hydrochloric acid, ethanol, acetone and water [38]. The methanol extract of papaya peel also showed antibacterial against *S. aureus* [39].

100 mg mL^{-1} of aqueous extract of papaya peel showed antibacterial against *S. aureus, P. aeruginosa* and *E. coli*. While 100 mg mL^{-1} of aqueous extract of papaya seed only showed activity against *S. aureus* and *E. coli* [40].

Ethanol extract of ripe papaya seeds showed antibacterial against *S. choleraesuis* and *S. aureus,* but no activity was found in *E. coli,* and *K. pneumoniae* [41]. Aqueous and 70% methanolic extract of papaya seed was investigated by Peter, Kumar [42] for antibacterial activity of *S. aureus, P. aeruginosa, E. coli* and *Salmonella typhi* and it was observed that the extracts were able to inhibit all the bacteria test.

Anti-fungal properties

Velázquez-Nuñez, Avila-Sosa [43] studied antifungal activity of essential oil from orange peels (*Citrus sinensis* var. Valencia) by compared two exposure methods (vapour exposure or direct addition) of the oil on the growth of *Aspergillus flavus.* The result showed that the vapour was more effective to inhibit the activity since the concentration of the oil for vapours to show the same antifungal effect with direct addition was much lower.

Ethyl acetate, petroleum ether, ethanol extracts of orange peels inhibited *Valsa mali*; with inhibitory rates above 90%, while the inhibitory rates of the ethyl acetate and ethanol extracts on *Botrytis cinerea*, the ethyl acetate and petroleum ether extracts on *Pythium aphanidermatum*, and the petroleum ether extract on *Alternaria alternate* were all above 70% [44].

Aqueous and methanol extracts of strawberry pomace were found to inhibit the growth of *Candida* species: *C. krusei, C. albicans, C. parapsilosis, C. glabrata* and *C. pulcherrima* [23].

Extract of ripe and unripe papaya seed also showed significant antifungal activity by inhibited activity of *Rhizopus* spp, *Aspergillus* spp and *Mucor* spp. [45]. The methanol extract of the papaya seed and isolated compound, 2,3,4-trihydroxytoluene (200 $\mu g\ ml^{-1}$) showed antifungal activity against *Candida albicans, Aspergillus flavus* and *Penicillium citrinium* [46].

Mango seed kernel showed antifungal activity against *A. niger* and *C. albicans* [35].

Anticancer properties

Ethanol extracts of orange peel, banana peel and watermelon peel showed cytotoxic activity on human breast carcinoma (MCF-7) cell line. However, the mechanism of the activity was not studied [22].

Apple

The crude extract from material left over after juice extraction of apple was found to be affecting the three biomarkers of colon cancer risk no cytotoxic

effects. The crude extract decreased DNA damage (associated with tumour initiation), enhanced colonic barrier function (associated with decreasing tumour promotion) and reduced invasive potential (associated with reduced tumour metastatic potential) [47].

Nonextractable polyphenols (NEPPs) from frozen industrial apple waste by-products (1 mg ml^{-1}) had higher inhibitory effects against HeLa, HepG2 and human colon cancer cells (HT-29) than the extractable polyphenols (EPPs) [48]. However, the mechanism is not yet known.

Apple pomace of Granny Smith variety showed antiproliferative activities on HeLa, HT-29 and MCF7 cell lines with the IC_{50} of HeLa, HT-29 and MCF7 values were 26.40 mg ml^{-1}, 22.47 mg ml^{-1} and 21.26 mg ml^{-1}, respectively [49]. The mechanism is not yet known.

The fresh apple peel extract was found to inhibit the formation of keratoacanthomas and squamous cell carcinomas in the mouse skin model. The apple peel extract inhibited tumorigenesis via free radical scavenging action and an inhibition of AP-1-MAPK signalling. The fresh apple peel extract was a potent scavenger of $^{\bullet}OH$ (hydroxyl) and superoxide radicals. It also inhibited AP-1 (activator protein-1) activation and phosphorylation of MAPK (mitogen-activated protein kinase) induced by UV irradiation or TPA (12-*O*-tetradecanolyphorbol-13-acetate) stimulation in an epidermal cell line and transgenic animals [50].

Apple peel extract (APE) of organic Gala apples was found to decrease in growth and clonogenic survival of human prostate carcinoma CWR22Rv1 and DU145 cells and breast carcinoma MCF7 and MCF-7:Her18 cells. With concentration-dependent, APE decreased the protein levels of proliferative cell nuclear antigen and also increased the maspin, a tumour suppressor protein that negatively regulates cell invasion, metastasis, and angiogenesis [51].

Apple peels from different varieties (Rome Beauty, Idared, Cortland, and Golden Delicious) were found to be inhibited the growth of liver tumour cells [52]. However, the mechanism of the action was not studied.

The apple flavonoid-enriched fraction (AF4) isolated from the apple peels (Northern Spy variety) inhibited the cell growth of HepG2 cells in a time- and dose-dependent manner. AF4 induced apoptosis in HepG2 cells within 6 h of treatment via activation of caspase-3. AF4 also induced G2/M phase arrest and acted as a strong DNA topoisomerase II catalytic inhibitor to drive the cells to apoptosis [53].

Twelve triterpenoids isolated from apple peels have potent antiproliferative activity against MCF-7, Caco-2 and HepG2 cells. 2α-hydroxyursolic acid, 3β-*trans-p*-coumaroyloxy-2α-hydroxyolean-12-en-28-oic acid and 2α-hydroxy-3β-{[(2*E*)-3-phenyl-1-oxo-2-propenyl]oxy}olean-12-en-28-oic acid showed higher antiproliferative activity against HepG2 cancer cells with EC_{50} values of 10.56 ± 1.44, 20.58 ± 1.32, and 17.94 ± 2.56 μM, respectively. Ursolic acid, 2α-hydroxyursolic acid, 2α-hydroxy-3β-{[(2*E*)-3-phenyl-1-oxo-2-propenyl]oxy}olean-12-en-28-oic acid and 3β-*trans-p*-coumaroyloxy-2α-hydroxyolean-12-en-28-oic acid exhibited antiproliferative activity against MCF-7 cancer cells with EC_{50} values of 14.40 ± 1.80, 4.70 ± 1.70, 29.20 ± 3.30 and 20.90 ± 2.30 μM, respectively. All triterpenoids tested exhibited antiproliferative activity against Caco-2 cancer cells with EC_{50} values of <60 μM [54]. The mechanism is not yet known.

Oleanic, ursanic and lupanic pentacyclic triterpenoids isolated from apple peel was reported to show anti-inflammatory effects. They acted on IP-10 gene expression, which plays an important role in inflammation and inflammatory bowel disease [55].

Orange

Polymethoxyflavones (PMFs) from sweet orange (*Citrus sinensis* L.) peel were found to exert antiproliferative and proapoptotic activity in human breast cancer cells. The PMFs induced apoptosis by triggering an increase in $[Ca^{2+}]$, followed by the activation of Ca^{2+}-dependent apoptotic proteases, l-calpain and caspase-12. The hydroxylation of PMFs, particularly the C-5 hydroxyl group, is critical for enhancing their proapoptotic activity [56].

Three major 5-hydroxy PMFs, which are 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone,

5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone and 5-hydroxy-6,7,8,4′-tetramethoxyflavone showed much stronger inhibitory effects on the growth of colon cancer cells compared to their permethoxylated counterparts. This showed that suggesting hydroxyl group at 5-position play a role in enhancing the inhibitory activity. However, three 5-hydroxy PMFs inhibited colon cancer cell growth by different mechanisms, where 5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone caused the cell cycle arrest at the G2/M phase in HT29 cells, while 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone led to G0/G1 phase arrest. In contrast, 5-hydroxy-6,7,8,4′-tetramethoxyflavone increased sub-G0/G1 cell population, which has been confirmed to be due to enhanced apoptosis. Besides that, the inhibitory effects of 5-hydroxy PMFs were also associated with their ability in modulating key signalling proteins related to cell proliferation and apoptosis, including CDK-2, CDK-4, $p21^{Cip1/Waf1}$, caspases 3 and 8, phosphor-Rb, Mcl-1 and poly ADP ribose polymerase (PARP) [57].

Four pure PMFs (nobiletin, 3,5,6,7,8,39,49-heptamethoxyflavone (HMF), 5-hydroxy-3,6,7,8,39,49-hexamethoxyflavone (5HHMF) and 5-hydroxy-3,7,8,39,49-pentamethoxyflavone (5HPMF)) isolated from sweet orange peel were studied on growth of human lung cancer cells H1299. Hydroxylated PMFs, i. e., 5HPMF and 5HHMF, showed the much stronger inhibitory effect on H1299 cell growth than their permethoxylated counterparts, i. e., nobiletin and HMF, respectively. 5HPMF and 5HHMF caused a significant increase in sub-G0/G1 phase whereas the permethoxylated counterpart PMFs did not affect the cell cycle distribution at same concentrations tested. 5HPMF and 5HHMF downregulated oncogenic proteins including iNOS, COX-2, Mcl-1, and K-ras. The compounds also induced apoptosis by activated the caspase-3 and cleavage of PARP [58].

Water extract of sweet orange peel (WESP) prevents the cytotoxicity of HepG2 cells induced by *tert*-butyl-hydroperoxide (*t*-BHP). WESP scavenged reactive oxygen species (ROS) in *t*-BHP-induced HepG2 cells, decreased ROS generation and lipid peroxidation, as well as with up-regulation of glutathione (GSH) levels and antioxidant enzyme activity. Direct scavenger of ROS by WESP regulated the expression of Bcl-2 family proteins, mitochondrial function and caspase activity [59].

The exact amount of 0.5% orange peels extract in the new Western-style diet (NWD) was shown to decrease the development of tumours, with multiplicity decreasing 49% in the small intestine and 38% in the colon and also increased apoptosis in tumours of the small and large intestine [60]. In addition, orange peels extract with 30% of polymethoxyflavones (PMFs) have increased apoptosis and decreased the development of typical hyperplastic lesion in ductal epithelial cells of mouse mammary gland [61].

Hesperidin isolated from the peel of *Citrus sinensis* was found effectively exhibit anticancer activity against the larynx, cervix, breast and liver carcinoma cell lines with IC_{50} 1.67, 3.33, 4.17 and 4.58 μg mL^{-1}, respectively [62]. However, the mechanism of the action of this activity was not studied.

Rambutan

Methanol extracts of rambutan seed and pericarp showed significant cytotoxicity effect to human mouth carcinoma (CLS-354) with IC_{50} values of 305 and 292 μg mL^{-1}, respectively. In addition, both extracts had toxicity effect to human peripheral blood mononuclear cells (PBMCS) [63]. However, the mechanism of action of this cytotoxicity effect is still unknown.

Purified *N. lappaceum* trypsin inhibitor possessed an inhibitory effect on the growth of MCF-7 (IC_{50} = 130.7 μM), HepG2 (IC_{50} = 215.3 μM), CNE-1 (IC_{50} = 277.0 μM), and CNE-2 (IC_{50} = 30.0 μM) tumor cell lines, whereas no significant effect was observed on HEN-2 and SUME-α cells [1]. However, the mechanisms of the action were not yet studied.

The methanolic yellow and red rambutan peel extract exhibited activity against breast cancer cell line (MDA-MB-231) and osteosarcoma cell line (MG-63). The IC_{50} value for MDA-MB-231 and MG-63 cancer cell lines that had been treated with yellow were 5.42 and 6.87 μg mL^{-1}, respectively and with red were 12.4 and 13.95 μg mL^{-1}, respectively [64].

The mechanisms of this action were also unknown.

Mango

The mango seed kernel extracts increased apoptotic markers in MCF-7 and MDA-MB-231 cells, by increasing the pro-apoptotic factors (Bax, cytochrome c, p53 and caspases). Besides that, the extracts also reduced the pro-survival factors (GSH and Bcl-2) in the cancer cells. All these activities had proof that the mango kernel extract has anticancer properties [65, 66].

Mango peel was found to effectively inhibited proliferation in human gastric cancer AGS cells, HeLa cells, HepG2 cells [67], MCF-7 cells [68, 69] and MDA-MB-231 cells [69]. Mango peel inhibits the proliferation of HeLa cells via a mechanism involving the induction of apoptosis by the down-regulation of Bcl-2 and activation of caspases-3, -8 and -9 [70]. It also affected the Ca^{2+} signalling in MCF-7 cells [71].

Gallotannin-rich extracts from mango kernel and peel showed antiproliferative activity on the MDA-MB-231 breast, HepG2 liver, and HL-60 leukaemia cells but the mechanisms of the activity were not studied [72].

Grape

Grape peel and pomace inhibited tNOX and growth of HeLa cells and also inhibited the growth of 4T1 mammary tumours in situ in mice [73]. Grape pomace also inhibited the proliferation of Caco-2 and HT-29 colon cancer cells by induced apoptosis via caspase-3 expression and DNA fragmentation [74].

Grape seed extract (GSE) enhancing the growth and viability of normal cell and induced apoptotic cell death in MCF-7, lung cancer, gastric adenocarcinoma and human prostate cancer (PCA) cells [75, 76]. GSE causes mitochondrial damage leading to cytochrome *c* release in cytosol and activation of caspases 3 and caspases 9 resulting in PARP cleavage. GSE also was found to induce apoptosis in a JB6 C141 cell (a well-developed cell culture model for studying tumour promotion in keratinocytes) through a p53-dependent pathway and involved its target proteins of the bcl-2 family (Bax and Bcl-2) and activation of caspase 3 [77].

GSE induced apoptosis, and inhibit tumour growth and metastasis of highly metastatic breast cancer cells through disruption of mitochondrial pathway and increased activation of caspase 3 [78]. A study by Sharma, Tyagi [79] shown that combination of seed extract with doxorubicin (a chemotherapy drug) have caused apoptotic death to breast cancer cells but the mechanism of the action was not studied. GSE inhibited vascular endothelial growth factor (VEGF) of messenger RNA (mRNA), protein expression in U251 human glioma cells and MDA-MB-231 human breast cancer cells via reducing HIF-1α protein synthesis through blocking Akt activation [80].

In PCA, GSE mediated anticancer effect via impairment of EGFR–ERK1/2–Elk1–AP1-mediated mitogenic signalling and activation of JNK causing growth inhibition and apoptosis [81]. Polyphenolic fraction isolated from grape seed inhibited the cell growth of PCA, and this effect involves the modulation of mitogenic signalling and cell-cycle regulators and induction of G1 arrest and apoptotic death [82]. Procyanidin B2-3,3′-di-O-gallate was found to be major active constituent causing growth inhibition and apoptotic death of PCA cells [83].

GSE also showed strong growth inhibitory and apoptosis-inducing effects against human colon carcinoma cells [84-87]. The mechanism involves in this activity were the down-regulation of COX-2, iNOS and β-catenin, cyclin D1 and c-Myc expression and up-regulation of Cip1/p21 [88]. GSE upregulates p21 expression via ROS-mediated ERK1/2 activation and GSE-induced p21 level, in part, mediates GSE-induced G_1 arrest. However, the GSE does not affect transcriptional or posttranslational mechanisms but modulates posttranscriptional and translational mechanisms for the upregulation of p21 expression [89]. GSE also decreased focal adhesion kinase levels, increase in caspase-3, caspase-9 and poly(ADP-ribose) polymerase cleavage, and caused DNA damage-induced activation of ataia telangiectasia mutated kinase and Chk2 as well as p53 Ser^{15} phosphorylation and its translocation to mitochondria [90]. The GSE also showed the mechanism of apoptosis via loss of

mitochondrial membrane potential, increased levels of Bcl-2 and suppression of caspase-3 activation [91, 92].

GSE showed strong growth inhibitory and apoptosis-inducing effects against human epidermoid carcinoma A431 cells [93]. In ovarian cancer chemotherapy treatment, GSE could reverse multi-drug resistance (MDR) in A2780/T cells by inhibited the function and expression of P-gp. The GSE also inhibited P-gp expression in A2780/T cells via the suppression of NF-κB activity and MAPK/ERK pathway mediated YB-1 activation [94].

In the *in-vivo* study, GSE showed chemoprotective activity in a rat model of breast cancer [95]. GSE also inhibited prostate cancer growth and progression in transgenic adenocarcinoma of the mouse prostate (TRAMP) mice via apoptosis and suppression of cell cycle progression and cell proliferation [96]. In human non-small cell lung cancer (NSCLC) tumour xenografts of athymic nude mice, GSE inhibited tumour cell proliferation, angiogenesis and up-regulation of insulin-like growth factor binding protein-3 [97]. GSE also showed activity in inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced edema, hyperplasia, leukocytes infiltration, myeloperoxidase, COX-2 expression and PGE2 production in the mouse skin [98]. In the anti-tumor-promotion study, 7,12-dimethylbenz[*a*]anthracene (DMBA)-initiated and 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-promoted SENCAR mouse skin two-stage carcinogenesis protocol was used as a model system, and the result showed that the polyphenolic fraction isolated from grape seed showed protection against tumour promotion in the mouse skin tumorigenesis model. However, the mechanism of this activity was not studied [99].

Papaya

Papaya peel extract possessed anticancer activity against human hepatoma (HepG2) cell line [100, 101] by inducing antioxidant enzymes, lowering cancer cell viability and inducing apoptosis. The extract induced apoptosis by lowering COX-2 activity enhanced caspase-3 activity and induced DNA fragmentation [100].

Anti-diabetic properties

Apple

Peel extract of four varieties apples (Cortland, McIntosh, Empire and Mutsu) were found to inhibit α-glucosidase activity. The study has proven that the phenolic content in the apples had strong ties to the activities via inhibition of starch hydrolyzing enzymes and antioxidant activity [102]. Egyptian Anna Apple peel extract was reported to possess antihyperglycemic effects by reduction of the inflammatory response, mitigation of the oxidative stress, and normalisation of the deranged lipid profile. Besides that, expression of inflammatory cytokines had been inhibited by the suppression of NF-kB activity which modulated the antioxidant impact [103].

Strawberry

Strawberry pomace from Marmolada cultivar showed α-glucosidase inhibitory potential with EC_{50} 1.16 mg ml^{-1} while strawberry pomace from Clery cultivar showed α-glucosidase inhibitory potential with EC_{50} 1.24 mg ml^{-1} [104]. Ellagitanins from strawberry pomace decreased postprandial glycaemia in rats by mitigated glucose-, starch- or sucrose-induced postprandial glycemic load. It also decreased the activities of mucosal sucrose and maltase in the jejunum [105].

Watermelon

One percent of watermelon rind ethanol extract (WM-E) significantly decreased blood glucose level and increased serum insulin levels in STZ-diabetic mice. The antidiabetic activities of WM-E were more effective than the group treated with 10% watermelon flesh powder [106]. However, the mechanism of the action was not studied.

Rambutan

Rambutan peels extract, and fractions (hexane, ethyl acetate, butanol and water) showed high α-glucosidase inhibitor activity with IC_{50} 9.92, 16.20, 10.43, 12.67 and 14.18 mg ml^{-1}, respectively. This showed that the extract and fractions have potential

as hypoglycemic agent [107]. Ethanol extract of rambutan peel also showed α-glucosidase-inhibitory-activity and β-glucosidase inhibitory activity with IC_{50} values 0.106 and 7.02 μg ml^{-1}, respectively [108]. The hydroethanolic rambutan rind extract and isolated tannin possessed inhibitory effects on α-amylase and α-glucosidase activities with maximum percentage inhibition of α-amylase enzyme activity by the extract and tannin were obtained at a concentration of 2.50 mg ml^{-1} (97.30% and 95.65%, respectively). While, the maximum percentage inhibition of α-glucosidase enzyme activity by the extract and tannin were obtained at a concentration of 2.50 mg ml^{-1} (96.66%) and 5 mg ml^{-1} (95.79%), respectively [109].

In *in vivo* study using rat model, rambutan peel extract with dose 500 mg kg^{-1} had showed the reduced glucose levels at 61.76% [110]. Another study showed that the ethanol extract of rambutan peel with a dose of 125, 250, and 500 mg kg^{-1} had blood glucose lowering activity in mice induced alloxan with the percentage decrease in blood glucose levels at 22.65%, 49.05% and 61.76%, respectively [111]. Rambutan seed infusion also showed the effect of reducing blood glucose level, and body weight of mice induces with alloxan tetrahydrate [112]. The mechanism of this action is not yet known.

Papaya

Seed and peel of unripe papaya showed inhibitory activities against α-amylase, α-glucosidase and SNP-induced lipid peroxidation in rat pancreas. The IC_{50} value of α-amylase, α-glucosidase and SNP-induced lipid peroxidation in rat pancreas seed were 1.11, 2.52 and 2.42 mg ml^{-1}, respectively. While, the IC_{50} value of α-amylase, α-glucosidase and SNP-induced lipid peroxidation in rat pancreas peel were 0.96, 2.64 and 2.23 mg ml^{-1}, respectively [113]. Besides that, the papaya seed extract demonstrated the hypoglycemic, hypolipidemic and cardioprotective potentials in normal rats by lowering the concentration of fasting blood glucose, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, low-density lipoprotein cholesterol and high-density cholesterol [114]. However, the mechanism is not yet known.

Mango

The peel and fibrous pulp waste of mango decreased total starch digestibility, showed the final rate of amylolysis of mashed potatoes as the starch source and caused the glucose diffusion retarded, suggested that this by-product can be used in controlling plasma glucose [115]. The mango peel extract also inhibited α-amylase and α-glucosidase activities, with IC_{50} values of 4.0 and 3.5 μg ml^{-1}, respectively.

Mango peel extract can decrease fasting blood glucose, fructosamine and glycated haemoglobin levels, increased plasma insulin level and decreased malondialdehyde level, but increased the activities of antioxidant enzymes significantly in liver and kidney in streptozotocin-induced diabetic rats. These showed that the mango peel could ameliorate diabetes [116]. The extract also was found to ameliorated hyperglycaemia, hyperlipidaemia and nephroprotective properties in streptozotocin-induced diabetic rats [117]. The mechanism is not yet known.

Grape

Red and white grape pomace extracts inhibited yeast α-glucosidase activity by 63.9% and 42.4%, respectively. The extracts also inhibited rat intestinal α-glucosidase activity by 47% and 39%, respectively. *In vivo* study, showed that red grape pomace extract at 400 mg kg^{-1} suppressed postprandial hyperglycemia in STZ-induced mice [118]. Combination of 0.3% grape pomace with 0.05% omija fruit extract in diet lowered the levels of HbA_{1c}, blood and plasma glucose and also insulin and homoeostasis model assessment of insulin resistance (HOMA-IR), decreased hepatic gluconeogenic enzymes activities and adiposity and also improved preservation of pancreatic β-cells in type 2 diabetic *db/db* mice [119].

The extract of grape seed procyanidins showed antihyperglycemic property with insulin-mimetic properties by stimulated glucose uptake in L6E9 myotubes and 3T3-L1 adipocytes. It also stimulated glucose transporter-4 translocation to the plasma membrane [120]. Besides antihyperglycemic effect, GSPE also increased serum insulin and pancreatic glutathione (GSH) levels, reduced lipid peroxidation and

ameliorated the damage to pancreatic tissue [121]. The GSPE showed anti-diabetic effect through normal insulin secretion from the remnant beta cells and alleviated endoplasmic reticulum (ER) stress possibly via restoration of moderate dilatation of ER and inhibition of some ER stress markers in the diabetic pancreas [122].

GSPE was reported to have potential in preventing and treating vascular complications of diabetes mellitus. One of that study reported that GSPE showed protective effects on the aorta of diabetic rat. It caused high aortic recovery by regulating the processes of reversible proteins that involved oxidative stress, cell proliferation and apoptosis, inflammatory pathways and substance metabolism [123]. Another study reported that GSPE inhibited AGE-induced proliferation and migration of human aortic smooth muscle cells (HASMCs), upregulated the protein level of ubiquitin COOH-terminal hydrolase 1 (UCH-L1) and attenuated the degradation of IκB-α and nuclear translocation of NF-κB by modulating ubiquitination of IκB-α in AGE-exposed HASMCs [124].

GSE improved markers of inflammation and glycaemia and a sole marker of oxidative stress in obese Type 2 diabetic patients [125, 126]. GSPE showed protection in diabetic neuropathy by improved the decreased mechanical allodynia and sciatic-tibial nerve conductive velocity and alleviated nerve impairment of diabetic rate [127]. It also caused high advanced glycation end products (AGEs) recovery mainly by regulating oxidative stress, glycosylation damage, and amino acids metabolism [128]. Besides decreased serum AGEs, GSPE also downregulated over the expression of the receptor for advanced glycation end products (RAGE) and connective tissue growth factor (CTGF) [129]. GSPE also ameliorated diabetic nephropathy rats through reduction of oxidative stress and increased in renal antioxidant enzyme activity [130].

Besides that, the GSPE plays an important role against diabetic cardiomyopathy by reduced the levels of RAGE, nuclear factor-κB (NF-κB), and transforming growth factor-β_1 (TGF-β_1) mRNA transcription in the myocardial tissue of diabetic rats, decreased the number of degenerated mitochondria and improved the preservation of the fine structure of the left ventricular myocardium [131].

GSE also showed potential to inhibit α-glucosidase and α-amylase activity with IC_{50} values of 1.2 and 8.7 μg ml^{-1}, respectively [132]. Grape seed polyphenols showed protective effects against high glucose-induced cytotoxicity in cultured LLC-PK_1 (porcine proximal tubule cell line) cells by inhibited nuclear translocation of nuclear factor-kappa B and the expression levels of inducible nitric oxide synthase, cyclooxygenase-2 and bax [133].

Anti-inflammatory properties

3′,4′,3,5,6,7,8-heptamethoxyflavone (HMF), a citrus polymethoxylated flavone isolated from orange peel oil did not show anti-inflammatory properties in the bacterial lipopolysaccharide (LPS)-challenge/tumour necrosis factor-α (TNFα) response in mice and in the carrageenan/paw edema assay in rats [134].

Fractions (API-VI) recovered from polyphenol-enriched extract of industrial apple pomace were study for inhibitory effects on cyclooxygenase-2 (COX-2) expression in lipopolysaccharides (LPS)-induced mouse RAW 264.7 cell line to studies their anti-inflammatory effects and the result showed that only APIII had the strongest activity against COX-2 expression at 5 μg ml^{-1} compare to other fractions [135].

Orange peel extract showed strong anti-inflammation activity against U-937 cells (CRL-1593.2, human histiocytic lymphoma) by strong down-regulation of inflammatory surrogate genes and also showed anti-inflammatory effects in the mouse paw edema *in vivo* model at dosages around 250 mg kg^{-1} [136].

Grape seed procyanidin extract (GSPE) exert an anti-inflammatory effect on RAW 264.7 macrophages stimulated with lipopolysaccharide plus interferon-γ by inhibiting iNOS expression at the transcriptional level by suppression of the NFκB signalling pathway. [137] In rat fed high-fat diet, the GSPE also showed anti-inflammatory activity by adjusting adipose tissue cytokine imbalance, enhancing anti-inflammatory molecules (C-reactive protein, IL-6 and TNF-α) and diminishing proinflammatory ones [138]. GSPE have

potential to attenuate UVB-induced oxidative stress via inhibition of UVB-induced phosphorylation of extracellular signal-regulated kinase ½ and c-Jun-NH2-kinase. It also mediated p38 proteins of MAPK family through reactivation of MAPK phosphatases. GSPE inhibited UVB-induced activation of NF-κB/p65 through inhibition of degradation of IκBα and activation of IκB kinase α (IKKα) [139].

GSPE also have potential to ameliorate inflammatory bowel disease indices, increased colonic goblet cell numbers and decreased myeloperoxidase levels in the large intestine. It decreased inflammation and the expression of pore-forming tight junction protein claudin2, and also increased the levels of *Lactobacilli* and *Bacteroides* in the gut microbiota of IL10KO mice [140].

Grape procyanidins prevent both systemic and local low-grade inflammation in adipose tissue, muscle and liver by reduced plasmatic systemic markers of inflammation tumour necrosis factor-α (TNF-α) and C-reactive protein (CRP) [141].

Antihypercholesterol properties

The rambutan peel [110, 111], papaya seed, grape pomace and seed [142-146] and apple pomace [143] extracts had potential to be used in the management of hypercholesterolaemia due to its ability to lower total cholesterol. Papaya seed extract and grape pomace extract lower LDL and triglycerides and also increased HDL level in hypercholesterolemic rats. Grape and apple pomace extracts reduced the activities of antioxidant enzymes superoxides dismutase, catalase and glutathione peroxidase in erythrocytes. The grape and apple pomace also reduced the HMG-CoA reductase activity in liver and increased the fractional catabolic rate of plasma cholesterol [143].

Grape seed tannins also showed the anti-hypercholesterolemic effect by enhancing reverse cholesterol transport and increasing acid excretion [147]. For the extract of grape seed proanthocyanidins, the extract improved dyslipidemia associated with high-fed diet, mainly by repressing lipogenesis and very low-density lipoprotein assembly in the liver [148]. The antihypercholesterolemic activity by grape seed proanthocyanidins extract was mediated by enhancement of bile acid excretion and up-regulation of CYP7A1 [149]. The extract also improved the antioxidant status and lipid levels and also controlled apoptosis, proving its anti-oxidant, anti-lipid peroxidative, and anti-apoptotic property on cholesterol and cholic acid-induced hypercholesterolemia model [150].

Anti-obesity properties

Orange peel extract was reported to have anti-obesity effect by suppressing body weight gain and adipose tissue formation [151].

The dietary grape pomace extract supplementation showed anti-inflammatory activity in high fat diet-induced obese mice. However, the extract in the high-fat diet did not affect the body weight [152]. While, in the study of GSE on high-fat-diet-induced obese mice, the grape seed extract possesses potential anti-obesity by decreased the body weight and normalised the epididymal and back fat weights, lipid concentrations, and carnitine levels through controlling lipid metabolism [153].

Rambutan peel extracts have potential as anti-obesity. Ethanol extract of rambutan peel decreased the expression of Insulin-Like Growth Factor-1 (Igf-1) and its receptor (Igf-1R) in the obese rat model [154]. The inhibition of Igf-1 and its receptor at the early process is the precise step for the therapy of obesity [155]. Distillate aqueous extract of rambutan peel declined the level of triglycerides, size of the adipocyte, mRNA level of *FABP4* gene and PPARγ expression on obesity rat model [156].

Mango seed kernel extract (MSKE) also possessed anti-obesity activity. The extract decreased the activity of glycerol 2-phosphate dehydrogenase in 3T3-L1 adipocytes without eliciting cell cytotoxicity. It also inhibited cellular lipid accumulation through down-regulation of transcription factors such as PPARγ and C/EBPα. Besides that, rats fed the high-fat diet containing 1% MSKE gained less weight, and their visceral fat mass tended to be lower than rats fed the high-fat diet alone. This showed that the MSKE exerts anti-obesity action both *in vivo* and *in vitro* [157].

Mango peel extracts and fractions from Irwin and

Nam Doc Mai cultivar were found to inhibit adipogenesis, a key process in the development of obesity. The extracts inhibit adipogenesis through the inhibition of mitotic clonal expansion [158, 159]. Lipophilic components, particularly free fatty acids were responsible for lipid accumulation promoting effects of peel extracts [159].

Prebiotic properties

Flours obtained from grapefruit albedo and peel, cactus pear peel and pineapple peel have been tested for prebiotic activity with two lactic acid bacteria strains (*P. pentosaceus* UAM21 and *A. viridans* UAM22). The flours were found to be fermentable carbon source by lactic acid bacteria with an acceptable short chain organic acids production [160].

Pectic oligosaccharides (POS) derived from orange peel can be effectively used as a prebiotic because POS fermentation caused an increase in the bifidobacteria and *Eubacterium rectale* numbers with the subsequent increase in butyrate concentrations [161].

Grape pomace extract induced a significant increase of *Lactobacillus acidophilus* CECT 903 biomass, showed that this extract could play a regulating role of intestinal tract microbiota, enhancing gastrointestinal health [162].

Other miscellaneous properties

Apple pomace extracts were evaluated for antiviral effect against herpes simplex virus type 1 (HSV-1) and 2 (HSV-2) and were found to inhibit both HSV-1 and HSV-2 replication in Vero cells by more than 50%, at non-cytotoxic concentrations [163].

25 mg kg^{-1} of *Citrus sinensis* (CS) peel extract was studied in L-T4 induced hyperthyroid animals for 10 days, and the study revealed the ameliorating potential of CS peel extract against various adverse effects of hyperthyroidism such as thyroxine-induced tissue lipid peroxidation and cardiac and renal hypertrophy. The extract also was found to alter concentrations of different serum lipids and glucose. The extract primarily acts through its antioxidative/free radical-scavenging, antithyroid and HDL-C stimulating properties [164].

Apple peel polyphenol-rich extract (APPE) was found to have an inhibitory effect on *H. pylori in vitro* [165] and *in vivo* [166] suggested that APPE exerts a protective effect, inhibiting the mechanism of cooperation between *H. pylori* and neutrophils that cause the gastric mucosa damage. Besides that, carotenoids: (all-E)-luteoxanthin, (all-E)-neoxanthin and (9′Z)-neoxanthin isolated from *Golden delicious* apple peel also showed potent anti-*H. pylori* activity [167].

Orange peel essential oil treatment can decrease oxidative injury in acute otitis media rats by decreased serum and cochlea malondialdehyde (MDA), increased antioxidant enzymes activities and decreased immunoglobulins A (IgA), immunoglobulins M (IgM) and immunoglobulins G (IgG) levels and [168].

Strawberry pomace was found to reduce serum and liver lipids and also alters gastrointestinal metabolite formation in fructose-fed rats [169]. Strawberry pomace also was found to show the effect on the enzymatic activity of intestinal microflora in rats by reducing the activity of β-glucuronidase in caecal digesta and faeces [170].

Hydro-alcoholic 70% extract from skin pomace of Alicante grape and seed pomace of Grenache and Syrah grape was found to possess an antihypertensive activity in spontaneously hypertensive rat (SHR) model [171].

5-(11′*Z*-heptadecenyl)-resorcinol and 5-(8′*Z*,11′*Z*-heptadecadienyl)-resorcinol isolated from mango peel were found to exhibit potent cyclooxygenase (COX)-1 and COX-2 inhibitory activity with IC_{50} values ranging from 1.9to 3.5 μM and from 3.5 to 4.4 μM, respectively [172].

200 mg kg^{-1} of methanol extract of banana peel suppressed the regrowth of ventral prostates and seminal vesicles induced by testosterone in castrated mice [173].

The effect of ethanol extract of watermelon rind on uterine smooth muscle was studied by evaluating the effects of contractile activity; spontaneous, those

elicited by potassium chloride (KCl) depolarization, or oxytocin (10 nmol l^{-1}) application in isolated rat uterus. The results showed that the 5mg ml^{-1} of extract decreased the uterine contractions via a nitric oxide-dependent mechanism and nitric oxide-cyclic guanosine monophosphate-dependent pathway [174].

Mango seed extracted in 50% ethanol, 95% ethanol and water possessed anti-allergic activity against antigen-induced β-hexosaminidase release as a marker of degranulation in RBL-2H3 cells with an IC_{50} value of 7.5, 21.5 and 40.4 μg ml^{-1}, respectively [13]. While alcoholic and aqueous seed kernel extract of mango showed anti-diarrhoeal activity by reduced intestinal motility and faecal score in Swiss albino mice [175, 176].

Mango peel extract was found to modulate endothelial cell migration, an essential step in the formation of new blood vessels or angiogenesis [177]. The purified *N. lappaceum* trypsin inhibitor exhibited HIV-1-RT inhibitory activity with an IC_{50} of 0.73 μM [1].

Peel of unripe and ripe papaya has potential to heal wounds on mice and influence the foetal growth and pregnancy of mice [178]. While the seed of ripe papaya showed the potential in heal wounds in Sprague-Dawley rats [41]. The grape seed proanthocyanidin extract promoted wound healing in Male BalbC mice [179].

Petroleum ether extract of the rind papaya showed anti-malarial activity again malaria strain *Plasmodim falciparum* FCK 2 *in vitro* with IC_{50} value 15.19 μg ml^{-1} [180]. On the other extracts, both aqueous and methanol extracts of papaya seed had shown antiulcer activity by reduced gastric secretion and protected the gastric mucosa from ethanol noxious effect in male rats [181-183]. Aqueous extract of papaya seed also showed the nephroprotective effect on CCl_4 renal injured rats and lessened the physiological and histopathological changes induced by gentamicin in rats [184]. Besides the aqueous extract, the ethanol extract also showed the nephroprotective effect [185].

The consumption of red wine grape pomace-rich in fibre and polyphenol antioxidants, as a food supplement in a regular diet, had shown to improved blood pressure, glycaemia and postprandial insulin and increased antioxidant defences and decreased oxidative protein damage indicating attenuation of oxidative stress in an adult human [186].

Grape seed extract had shown to exhibit a protective effect on acute gastric lesions in rats. This showed that the extract has potential as antiulcer agent [187]. Grape seed proanthocyanidin extract showed a protective effect against oxidative stress induced by cisplatin in rats by reduced cisplatin-induced the levels of thiobarbituric acid reactive substances in plasma, heart, kidney and liver, total lipid, cholesterol, urea and creatinine, and liver aspartate and alanine transaminases. It also ameliorated cisplatin-induced decrease in the activities of antioxidant enzymes, and reduced glutathione, total protein and albumin [188]. Grape seed proanthocyanidin extract also can attenuate acetaminophen-induced hepatic DNA damage, apoptotic and necrotic cell death of liver cells and antagonised the influence of an acetaminophen-induced change in bcl-X_L expression *in vivo*, showed that this extract has potential to have the hepatoprotective ability [189].

CONCLUSION

This review emphasises the importance of by-products from commonly consumes fruits for the nutritional, medicinal and pharmacological application. It is evident that these by-products had a wide range of nutritional, medicinal and pharmacological properties. Furthermore, a large number of by-products have shown antidiabetic and anticancer activity either *in vitro* or *in vivo* studies. Indeed, the mechanism of these properties should be investigated further in-depth. As diabetic and cancer causing thousands of death per year, hence the study on the applicability of these by-products may be helpful in future. The exploitation of by-products of fruits for the production of food additives or supplements with high nutritional value is a promising field as they are high-value products and their recovery may be economically attractive.

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CONFLICTS OF INTEREST

The author(s) declare that they have no competing interests.

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