Prophylactic Use of Natural Products against Developmentally Programmed Metabolic Syndrome

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ABSTRACT

Parental dietary choices and/or nutritional interventions in the offspring are critical to early life development, especially during the periods of active developmental plasticity in the offspring. Exposure to a high-fructose, high-fat diet during the fetal or neonatal period predisposes the affected individuals to the development of one or more features of metabolic syndrome, such as dyslipidemia, insulin resistance, diabetes, and associated cardiovascular diseases, later in their life. Owing to the increasing global prevalence of metabolic syndrome and multiple side effects that accompany conventional medicines, much attention is directed towards medicinal plants and phytochemicals as alternative interventions. Several studies have investigated the potential of natural agents to prevent programmed metabolic syndrome. This present review, therefore, highlights an inextricable relationship between the administration of medicinal plants or phytochemicals during the intrauterine or neonatal period, and the prevention of metabolic dysfunction in adulthood, while exploring the mechanisms by which they exert such an effect. The review also identifies plant products as a novel approach to the prevention and management of metabolic syndrome.

Introduction

The environment modifies the functions of biological systems. Exposure of the offspring to stressful conditions such as poor maternal diet during embryonic and/or fetal development exerts significant effects on the health of the affected individual [1]. Other environmental factors such as physical, social, psychological, occupational, or lifestyle stressors could equally program the individual for the risk of metabolic disorders later in adulthood [2]. One such disorder that could arise from early life perturbations is metabolic syndrome (MetS). MetS is a complex, multifactorial cluster of physiological and metabolically related factors, such as obesity, insulin resistance, and dyslipidemia, that collectively increase the risk of developing non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus, hypertension, and other cardiovascular diseases [3–5]. Globally, about two-thirds of deaths arising from noncommunicable diseases are mainly caused by MetS and related disorders [6]. Given the rising cases of obesity

and being overweight worldwide, MetS is considered to be a principal nutritional problem and one of the most extensively studied disorders associated with early life programming [7]. Obesity confers a significant risk for the development of MetS [8]. According to a recent report by the World Health Organization (WHO), over 1.9 billion adults aged 18 and above were estimated to be overweight worldwide, with about 650 million obese adults [9]. Despite recent therapeutic advances, the alarming increase in the global prevalence of MetS [10] constitutes a huge public health concern.

The concept of the developmental origins of health and disease provides a broader definition of the period of developmental plasticity to include the entire developmental period and not just the prenatal period [11, 12]. This period of developmental plasticity offers unique opportunities for prophylactic interventions to reverse the effects of programmed responses to an adverse environment in early life, a phenomenon known as reprogramming [13]. A number of studies have examined the potential of natural products as reprogramming strategies to prevent MetS [14–17]. Here, we review dietary phytochemical agents and plant extracts with prophylactic potential in programming and reprogramming against MetS. The authors systematically searched PubMed, SCOPUS, and Google Scholar for relevant studies until December 2020. The key words were "medicinal plant extracts and metabolic syndrome in offsprings", "maternal dietary supplements and offspring metabolic syndrome", "metabolic syndrome and phytochemicals", "neonatal intake", "supplement or phytochemicals", "high fat or high fructose induced metabolic dysfunction", "neonatal or fetal programming of metabolic dysfunction", "phytochemicals and neonatal programming of metabolic syndrome", "medicinal plant extracts and phytochemicals in programmed hypertension", "plant extracts and phytochemicals on non-alcoholic fatty liver disease", and "epigenetics and metabolic programming". The retrieved articles were thoroughly screened for eligibility while non-English papers were excluded.

Experimental and Epidemiological Evidence for the Developmental Origins of Metabolic Syndrome

Accumulating epidemiological and experimental studies provide compelling evidence for the developmental origins of MetS [18]. Epidemiological reports have associated adverse prenatal and postnatal environmental exposure to the development of MetS in adult life. Most of these epidemiological reports came from natural and man-made disasters, such as famine, which provided unique opportunities to study developmental programming in human populations [19, 20]. The Dutch famine (1944–1945) represents principal evidence for the developmental origins of MetS and is the most studied. Intrauterine exposure to poor nutrition due to the Dutch famine has been consistently associated with impaired metabolic phenotypes such as dyslipidemia, raised body mass index, obesity, and cardiovascular diseases [21–23]. Findings similar to those of the Dutch famine were also established in populations of other countries with data obtained from affected populations of the Austria famine [24], the Great Ukrainian famine (Holodomor) [25], Leningrad Siege [26], Chinese Great Leap Forward famine [27], Nigeria's Biafran war famine [28], Europe's Holocaust [29], and seasonal malnutrition in Spain [30], all of which occurred in the 20th century. In most of these studies, the initial exposure to poor nutrition in early life, as a result of the famine, was associated with the development of obesity, dyslipidemia, diabetes, hypertension, and other cardiovascular disorders in later life when compared to their control counterparts who were not exposed.

Furthermore, owing to the difficulties in developing animal models that present all the features of MetS [31], investigations into the developmental origin of MetS are done using models that manifest certain components of the syndrome. For instance, several animal studies have associated intrauterine protein and caloric restriction to the development of hypertension in adult offspring, as reviewed elsewhere [32]. Since poor nutrition also includes the intake of excess fat and calories, rodent models of maternal high-fat feeding during pregnancy have also been linked to the onset of hyperinsulinemia, glucose intolerance, endothelial dysfunction, and hypertension in adult offspring [33–35]. Further evidence came from a study that demonstrated an association between low-birth-weight neonates that experienced a catch-up growth and increased risk for the development of cardiovascular disease, one of the key complications of MetS [36]. These observations clearly indicate the link between adverse fetal and neonatal environments and the risk of developing MetS in adulthood.

Epigenetics and metabolic programming

The advent of epigenetics has provided an avenue for explaining the mechanisms by which environmental factors influence fetal and neonatal phenotypes as well as the subsequent development of diseases. Epigenetics is majorly concerned with heritable changes in DNA in the absence of structural modifications to the nucleotide sequence, enabling prompt regulation of gene expression in numerous cell types [37]. The developmental period is a time when the growing fetuses and neonates are prone to maternal and environmental stress that results in programmed morphological alterations, cellular responses, and gene expression that affect the metabolism and physiology of the offspring. The outcome of developmental programming may appear instantly, for instance, abnormal organ development or, later in adulthood, as impaired organ function [38]. A primary background that may form the basis of the latter scenario is traceable to the concept of the double hit hypothesis. The hypothesis states that a preliminary intervention usually regarded as "first hit" may sensitize an organ to produce physiological alterations [39, 40]. These alterations may manifest immediately, resulting in malfunctioned organs and eventual disease development or may be suppressed [41–44]. A second intervention (second hit) may unmask the suppressed effects or exacerbate the existing effects of the "first hit" [45, 46].

Suboptimal nutrition during the critical periods of developmental plasticity may alter gene expression via three different epigenetic mechanisms: (i) modification of the chromatin architecture and lysine and/or arginine residue at the N-terminal tails of histone [47], (ii) alteration in the availability of methyl groups

by distorting the activities of methyltransferase and DNA demethylation [48], and (iii) modification of expression levels of miRNA involved in regulating the principal proteins in the folate-mediated carbon metabolism pathway, which is known to regulate the metabolism of methionine, homocysteine, vitamin B complex, proteins, and histones as well as DNA and ribonucleic acid (RNA) [49–51].

The mechanisms of epigenetics include DNA methylation, modification of histones, packaging of chromatin, and alteration in non-coding RNA expression [52]. Adverse intrauterine milieu is translated into epigenetic modifications during gametogenesis and fetal development and are steadily preserved until adulthood [53]. These epigenetic modifications alter the expression of genes and hence the metabolic phenotype, producing diseases in adulthood.

Potential mechanism by which natural products reprogram against metabolic syndrome of developmental origin

The mechanism by which natural products offer protection against developmentally programmed MetS is poorly understood. Epigenetic mechanisms have been shown to play an important role in the regulation of cellular functions and are critical to the development of complex diseases, including MetS [54]. Epigenetic modification is a reversible process and can be achieved by diet, environment, and lifestyle choices [55]. Hence, epigenetic modification is suggested to play a role in the prophylactic effects of dietary phytochemicals [56]. The exact mechanism by which plant extracts and phytochemicals interact with the epigenome to modulate the expression of genes to protect against certain metabolic disorders has not been fully elucidated.

Several bioactive compounds derived from plants are epigenetic modulators [57]. For instance, polyphenols contained in green tea have been shown to improve the metabolism of offspring born to undernourished dams by modulating the expression of enzymes that influence epigenetic marks [58]. Although epigenetic modifications are rarely studied as potential preventive mechanisms that relate to the reprogramming effects of phytochemicals with the development of MetS, they have been implicated as a mechanism of prevention in non-programming models of some metabolic disorders [57]. Resveratrol protected the diabetic rat aorta from macroangiopathy by influencing DNA methylation [59]. Also, curcumin reportedly suppresses the hyperglycemia-induced inflammatory response via the modulation of histone acetylase and histone deacetylase activity [60]. In addition, phytochemicals have also been shown to improve metabolism by regulating the expression of microRNAs. Joven et al. [61] linked the inhibition of miR-103/107 by polyphenols from *Hibiscus sabdariffa* (HS) to improved glucose and lipid metabolism in hyperlipidemic mice. Similarly, quercetin and polyphenol extracts from HS and coffee prevented high-fat diet (HFD)-induced liver steatosis in mice via the upregulated expression of miR-122 [62].

Therefore, epigenetic mechanisms may explain the modification of gene expression by phytochemicals or medicinal extracts during the fetal and neonatal period of metabolically challenged rodents to protect against the development of MetS in adulthood. A potential mechanism by which medicinal plants and phytochemicals act during critical periods of developmental plasticity may modulate biological systems to prevent the development of MetS is summarized in ▶ **Fig. 1** below.

Phytochemicals and their classification

Phytochemicals are plant-sourced medicinal agents with fewer side effects compared to synthetic compounds [63]. They are broadly classified into phenolic compounds, terpenoids, and alkaloids including other nitrogen-containing plant constituents [64].

The phenolic compounds are the most abundant group of phytochemicals and are readily available in most plants. They include anthocyanins, anthochlors, benzofurans, chromones, coumarins, minor flavonoids, flavonones and flavonols, isoflavonoids, lignans, phenols and phenolic acids, phenolic ketones, phenylpropanoids, quinonoids, stilbenoids, tannins, and xanthones. Among these, flavonoids, phenolic acids, and polyphenols are the three major categories of dietary phenolics [65].

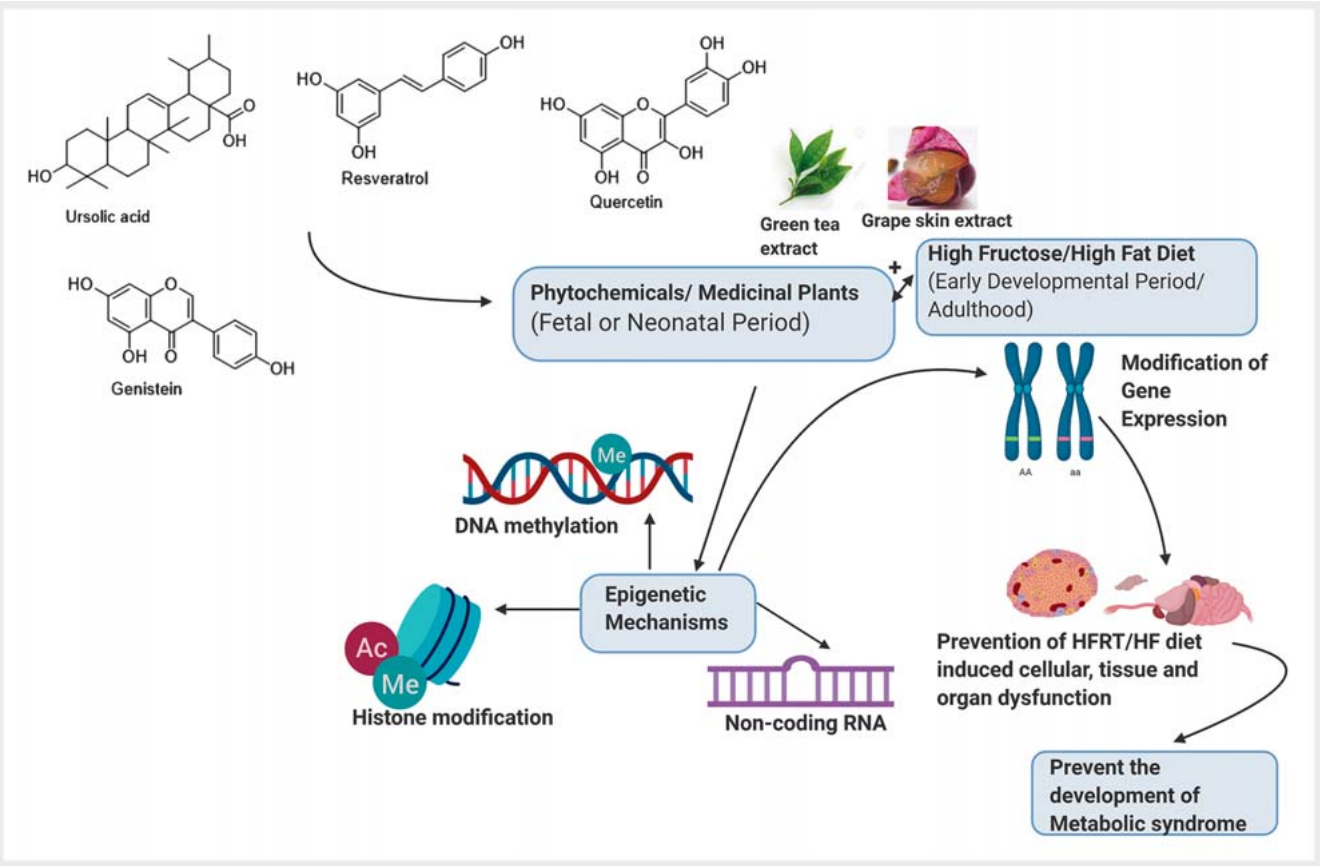
On the other hand, the terpenes (terpenoids), otherwise referred to as isoprenoids [66], are a class of natural products formed from five-carbon isoprene units. They include phytosterols (including β sitosterol), sesquiterpenes, monoterpenoids, hemiterpenoids, diterpenoids, triterpenoids, and saponins [67]. The third group, alkaloids, includes peptide, pyrrolidine and piperidine, pyrrolizidine, quinoline, betalain, indole, isoquinoline, lycopodium, quinolizidine, and tropane compounds. Other nitrogen-containing constituents include purines and pyrimidines, non-protein amino acids, and amines [67]. Most phytochemicals are sourced from fruits and vegetables and are classified according to their corresponding constituents as indicated in ▶ **Table 1** below. These phytochemicals have been investigated for their potential prophylactic activity against developmentally programmed MetS.

Beneficial Effects of Phytochemicals and Plant Extracts against Principal Features of Metabolic Syndrome

Dyslipidemia

Dyslipidemia is one of the hallmarks of MetS. It is characterized by abnormal lipid levels, usually presenting as an increased plasma concentration of low-density lipoprotein cholesterol (LDL-C) and triglycerides, coupled with low levels of high-density lipoprotein cholesterol (HDL-C) [68]. Reports from several experimental studies have improved the understanding of natural products and their mechanisms of action towards dyslipidemia. From existing studies (▶ **Table 2**), it is apparent that natural products offer long-term protection against MetS by targeting dyslipidemia, especially when introduced during the early periods of development. ▶ **Table 2** shows animal studies reporting on the beneficial effects of phytochemicals or plant extracts on lipid metabolism following a high-fructose (HF) diet or HFD [69–72].

The biosynthesis of lipids is a tightly regulated process. Sterol regulatory element binding transcription factor 1 (SREBP-1), peroxisome proliferator-activated receptor delta, and peroxisome



▶ **Fig. 1** Influence of medicinal plants and phytochemicals on metabolic programming. The figure illustrates the epigenetic mechanisms by which phytochemicals or extracts of medicinal plants may upregulate or downregulate the expression of genes associated with metabolism or its control, thereby preventing the development of MetS induced by a high-fructose or high-fat diet. HFRT = high fructose, HF = high fat, RNA = ribonucleic acid.

▶ **Table 1** Selected phytochemicals and their dietary sources.

Phytochemicals	Class	Subclass	Sources
Phytosterol	Terpenes		Vegetable oils (rapeseed oil), cereals, vegetables, fruits
Ursolic acid	Terpenes	Triterpenes	Apples, bilberries, peppermint, cranberries, elder flower, rosemary, lavender, thyme, hawthorn, oregano, prunes
Oleanolic acid	Terpenes	Triterpenes	Olives
Resveratrol	Phenolic compounds	Polyphenols	Grapes, wine, peanuts, soy
Curcumin	Phenolic compounds	Polyphenols	Tumeric, mustard
Quercetin	Phenolic compounds	Flavonoids	Cranberries, apples, onions, beans
Genistein	Phenolic compounds	Isoflavones	Soybean, fava beans, coffee, lupin
S-allyl cysteine	Nitrogen-containing compounds	Organosulphur	Garlic
Citrulline	Nitrogen-containing compounds	α-amino acid	Watermelon, legumes, nuts

proliferator-activated receptor gamma are key regulators of lipogenesis [73]. Fatty acid synthase (FAS), acetyl-coenzyme A carboxylase (ACC), adenosine triphosphate citrate lyase, and stearoyl-CoA desaturase-1 are the target genes of SREBP-1c in the lipogenic pathway [74]. Conversely, proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) and fibroblast growth factor 21 (FGF21) promote fatty acid oxidation and regulate lipid metabolism [75, 76]. Maternal supplementation of bitter melon

▶ **Table 2** Impact of various phytochemicals and plant extracts on features of metabolic syndrome.

Intervention	Experimental animal	Model	Duration of intervention	Age at evaluation	Measured parameters	Outcome	References
Bitter melon extract (1%)	Sprague-Dawley rats	Fetal programming (high fructose – 60%) Offspring weaned to high-fructose diet – 60% for 20 weeks	Throughout pregnancy and lactation	23 weeks	Serum CHO, TG, LW, hepatic TG and CHO, HLC, expression of SREBP-1, ACC2, FGF21, FABP 1, PPARα, PGC1α, antioxidant activities	Upregulation of PGC1α, FGF21, and FABP 1, which depicts enhanced lipid oxidation and a reduced lipogenesis, high antioxidant activity, reduced cholesterol and triglycerides	[77]
Oleanolic acid (60 mg/kg)	Sprague-Dawley rats	Neonatal programming (high-fructose solution – 20% w/v)	8 days (PND 7–14)	16 weeks	AMPK, GLUT-4, CPT-1, AdipoR1, AdipoR2, TNF-α, IL-6, VEGF, MCP-1, plasma adiponectin levels	Upregulated AMPK, Glut-4 gene, increased plasma adiponectin concentration	[80]
	Sprague-Dawley rats	Neonatal programming (first hit high-fructose solution – 20% w/v) Second hit (high fructose – 20% w/v) for 56 days (PND 56–112)	7 days (PND 7–13)	16 weeks (48 h earlier)	BM, visceral fat mass, epididymal fat mass, FPG, FPI, GTT, HOMA-IR	Protected against increase in TBM, prevented rise in AUC for OGTT, normalized FBG and HOMA-IR, prevented increase in plasma TG levels	[15]
	Sprague-Dawley rats	Neonatal programming (high-fructose solution – 20% w/v) Second hit (high fructose – 20% w/v) for 56 days (PND 56–112)	7 days (PND 7–13)	16 weeks	LFM, BM, LM HLC, HH, NAFLD score	Inhibited rise in BM, precluded increase in LM, blockage of hepatic lipid accumulation, prevented the occurrence of hepatic steatosis and fibrosis	[101]
Green tea extract (7.5 and 10 g/kg)	Sprague-Dawley rats	Fetal programming (high-fat diet)	Throughout pregnancy and lactation	13 weeks	FPG, FPI, index of IR, serum, muscle, and liver TG, serum leptin and adiponectin	Insulin resistance 57% lower, serum non-esterified fatty acid 23% lower, and liver TG was 26% lower, enhanced gene/protein expression related to lipid and glucose metabolism.	[16]
Grape skin extract (200 mg/kg)	Wistar rats	Fetal programming (high-fat diet 24%)	21 days (lactation period)	12 weeks 6 days; 25 weeks 5 days	FPG, FPI, HOMA-IR, plasma CHO, TG, BP, and vascular function, antioxidant activity	Protection against hypertriglyceridemia, hyperglycemia, lowered insulin resistance, inhibited increase in body weight, protection against hypertension	[17]
Phytosterol (2% solution)	Syrian Golden Hamsters	Fetal programming (high cholesterol – 0.5%)	Throughout pregnancy	3 weeks	Total-C, LDL-C, HDL-C, hepatic TG	Prevented hypercholesterolemia	[71]
Green tea extract (400 mg/kg)	Wistar rats	Fetal programming (high-fat diet)	Throughout pregnancy and lactation	13 weeks (OGTT – 12 weeks)	BW, serum analysis, OGTT, relative tissue weight, antioxidant enzyme activity, tissue cytokine levels, quantification of inflammatory protein	Prevented hypercholesterolemia, decreased levels of IL-10, IL-6, TNF-α, and IL-1β, and p-NF-κB p50 levels in gonadal adipose tissue	[69]

continued

▶ **Table 2** *Continued*

Intervention	Experimental animal	Model	Duration of intervention	Age at evaluation	Measured parameters	Outcome	References
Genistein (0.6 g/kg)	C57BL/6 mice	Fetal programming (high-fat diet – 60%)	21 days pre-pregnancy + Throughout Pregnancy and lactation	24 weeks	IngSAT, EpiVAT, OGTT, serum insulin, and lipid levels, gut microbiota	Decreased BG during GTT, FPI, VAT, and serum TG levels, increased HDL-C, enrichment of *Rikenella* as well as SCFA-producing bacteria such as *Alloprevotell*, *Odoribacter*, and *Clostridium* XlVa	[70]
Genistein (4, 40 and 160 mg/kg)	Sprague-Dawley rats	Neonatal programming (high-fat diet – 60%)	5 days	9 weeks	BW, LW, HH, hepatocyte apoptosis, plasma insulin, glucagon, ALT, expression of FAS, SREBP-1, PPARα, TNF-α	Decreased BW, inflammation and steatosis, reduced apoptosis, decreased FAS, SREBP-1, high PPARα (40 mg dose proved most effective)	[86]
Hibiscus sabdariffa calyx extract (50, 500 mg/kg)	Sprague-Dawley rats	Neonatal programming (high-fructose solution-20% w/v)	9 days (PND 4–14)	7 weeks 2 days (OGTT – 48 h earlier)	BM, OGTT, FPG, plasma insulin, TG, HOMA-IR	Normalized hypercholesterolemia in male and hypertriglyceridemia in female	[72]
Citrulline (2 g/kg)	Sprague-Dawley rats	Neonatal programming: pups from low-protein-fed dams – 4% throughout gestation, presented with high-fat diet challenge – 10% fructose w/v)	16 days (PND 6–21)	12 weeks 6 days	BW, plasma TG and HDL, insulin sensitivity index, liver TG, TC, FAS, SREBP1, HMGc1	Increased liver TG content, upregulated FAS and SREBP1, downregulation of HMGc1, no significant difference in BW, insulin sensitivity index, plasma TG and HDL	[88]
Resveratrol (200 mg/kg)	C57BL/6J mice	Fetal programming (high-fat diet – 45%)	Pregnancy + 21 days of lactation	11 weeks (GTT – 10 weeks)	LM, BAT, IngWAT & EpiWAT, GTT, metabolic parameters, histology of adipose tissue, AMPKα, P- AMPKα, cytochrome C, PPARγ, SIRT1	Increased metabolism in BAT of offspring, decreased adiposity and promotion of insulin sensitivity, rise in energy expenditure, facilitated BAT activity, and IngWAT browning	[14]
Resveratrol (2–2.5 mg/kg)	Wistar rats	Fetal programming (high fat 61.6%)	Throughout pregnancy and lactation	3 weeks	Serum CHO, LDL-C, HDL-C, TG and phospholipid, blood glucose, leptin levels, VAT, SCAT, expression of POMC, AGRP, NPY, and orexin, SIRT-1, oxidative stress	Protected against increased BW, leptin, VAT, SCAT, neuropeptides expression unaffected, elevated BG	[96]
Quercetin (50, 100 and 200 mg/kg)	Sprague-Dawley rats	Fetal programming (high-fat diet – 42% fat)	Throughout gestation and lactation	14 weeks 2 days	BW, Serum CHO, HDL-C, TG, IL-6, TNF-α	Prevention against increased BW, improved insulin sensitivity, prevention against hyperlipidemia, decreased inflammatory cytokines (IL-6)	[95]

continued

▶ **Table 2** *Continued*

Intervention	Experimental animal	Model	Duration of intervention	Age at evaluation	Measured parameters	Outcome	References
S-allyl cysteine (150 mg/kg)	Wistar rats	Neonatal programming (first hit- high fructose: 20% w/v) Second hit (high fructose: 20% w/v)	15 days (PND 6–20)	16 weeks (OGTT – 48 h earlier)	BM, OGTT and AUC, FPG, fasting plasma TG and CHO, degree of adiposity, LM, HLC, HH	Prevented hepatic lipid accumulation, prevented the development of micro-vesicular steatosis	[97]
	Wistar rats	Neonatal programming (high fructose 20% w/v)	15 days (PND 6–20)	3 weeks	TBM, non-fasted BG, TG, CHO, leptin and insulin concentrations and HOMA-IR, NAFLD scores	Increased insulin levels increased HOMA-IR in male, anti-insulinotropic effects in female	[98]
Resveratrol (50 mg/L)	Sprague-Dawley rats	Fetal programming high-fat – 58%, high sucrose (25% carbo-hydrate) + BPA (50 µg/kg)	Throughout pregnancy and lactation	16 weeks	Systolic BP, L-citrulline, L-arginine, ADMA, SDMA, NO_2^- levels oxidative stress-8-OHdG staining, renal eNOS, nNOS, AHR and target genes	Lowered systolic BP, increased L-arginine, NO_2^- levels, increased renal eNOS and nNOS protein levels, reduced 8-OHdG density, inhibition of AHR signaling pathway	[107]
Resveratrol (50 mg/L)	Sprague-Dawley rats	Fetal programming L-NAME (60 mg/kg), high-fat – 58%, high sucrose (25%) from weaning to adulthood	Throughout pregnancy and lactation	16 weeks	BP, L-citrulline, L-arginine, ADMA, SDMA, oxidative stress-8-OHdG, NO, gut microbiota composition	Significantly reduced systolic BP, and MAP, no effect on ADMA-NO pathway, reduced 8-OHdG density, modulated gut microbiota composition	[108]
Acai (*Euterpe oleracea* Mart) seed extract (200 mg/kg)	Wistar rats	Fetal programming (low-protein diet – 6% protein diet)	Throughout pregnancy	16 weeks	BP, vascular function, oxidative stress	Prevented programmed hypertension by reducing systolic BP, decreased plasma renin levels, prevented oxidative stress	[109]
Ursolic acid (10 mg/kg)	Sprague-Dawley rats	Neonatal programming (first hit – high fructose diet – 50%); Second hit (high fructose diet – 20%) 56 days (PND70-126)	14 days (PND 6–20)	18 weeks 3 days	Circulating TG, CHO and glucose, BM, total calorie intake and LFM, HLC, VF, HH	Reduced hepatic lipid accumulation, reduced hypertrophy, microvesicular and macrovesicular steatosis	[87]
Curcumin (500 mg/kg)	Sprague-Dawley rats	Neonatal programming (high-fructose solution – 20% w/v)	16 days	9 weeks	TBM and LM, HLC, steatosis scores, RNA expression of AMPKα: TNF-α	Decreased inflammation, inhibited upregulation of TNF-α, and downregulation of AMPKα	[100]

8-OHdG: 8-oxo-2′-deoxyguanosine; ACC2: acetyl-coenzyme A carboxylase beta; AdipoR1: adiponectin receptor 1; AdipoR2: adiponectin receptor 2; ADMA: asymmetric dimethylarginine; AGRP: agouti-related peptide; AHR: aryl hydrocarbon receptor; AMPK: 5′ adenosine monophosphate-activated protein kinase; ALT: alanine aminotransferase; AUC: area under curve; BAT: brown adipose tissue; BM: body mass; BP: blood pressure; BPA: bisphenol A; BW: body weight; CHO: cholesterol; CPT-1: carnitine palmitoyl transferase I; eNOS: endothelial nitric oxide synthase; EpiVAT: epididymal visceral adipose tissue; EpiWAT: epididymal white adipose tissue, FABP: fatty acid binding protein 1; FAS: fatty acid synthase; FGF21: fibroblast growth factor 21; FPG: fasting plasma glucose, FPI: fasting plasma insulin; GLUT-4: glucose transporter type 4; GTT: glucose tolerance test; HDL-C: high-density lipoprotein cholesterol; HH: hepatic histomorphometry; HLC: hepatic lipid content; HMGc1: high-mobility group cluster; HOMA-IR: homeostatic model assessment of insulin resistance; IL-6: interleukin 6; IngSAT: inguinal subcutaneous adipose tissue; IngWAT: inguinal white adipose tissue; IR: insulin resistance; LDL-C: low-density lipoprotein cholesterol; LFM: liver function markers; LM: liver mass; L-NAME: NG-nitro-L-arginine-methyl ester; LW: liver weight; MAP: mean arterial pressure; MCP: monocyte chemoattractant protein-1; NAFLD: non-alcoholic fatty liver disease; nNOS: neuronal nitric oxide synthase; NO: nitric oxide; NPY: neuropeptide Y; OGTT: oral glucose tolerance test; PGC1α: PPAR-gamma coactivator 1-alpha; PND: post-natal day; p-NF-κB p50: phosphorylated protein p50 subunit of nuclear factor kappa B; POMC: pro-opio-melanocortin; PPARα: peroxisome proliferator-activated receptor alpha; PPARγ: peroxisome proliferator-activated receptor gamma; SCFA: short chain fatty acid; SDMA: symmetric dimethylarginine; SIRT1: nicotinamide adenine dinucleotide-dependent deacetylase sirtuin-1; SREBP1: sterol regulatory element binding transcription factor 1; TBM: terminal body mass; TG: triglyceride; TOTAL-C: total cholesterol; VEGF: vascular endothelial growth factor

extract to HF-fed dams protected adult offspring against dyslipidemia via inhibition of lipogenesis and promotion of fatty acid oxidation [77]. The study by Ching et al. [77] demonstrated that this extract improved lipid metabolism via the downregulation of *Srebp1, Acc2*, and *Fas* expression levels and upregulated expression of *Pgc1α* and *Fgf21*.

In addition, adenosine monophosphate-activated protein kinase (AMPK) is a principal cellular regulator of metabolism known to activate catabolic pathways like *β*-oxidation and inhibit lipogenesis by modulating the expression of genes in the affected pathway [78, 79]. The administration of oleanolic acid (OA) in the neonatal period is believed to prevent dyslipidemia in adulthood through increased expression of *Ampk* [80]. These results suggest that plant extracts or phytochemicals acting during the critical window of developmental plasticity may target multiple genes involved in the biosynthesis and oxidation of fatty acids, thus facilitating improved lipid metabolism.

Furthermore, Zhou et al. [70] demonstrated that genistein, a phytochemical, prevents against hypertriglyceridemia and increases HDL-C levels in mice offsprings. Genistein also inhibited HFD-induced gut microbial dysbiosis. Certain intestinal bacteria such as *Alloprevotella odoribacter* and *Clostridium* XIVa have been established as being present in low quantities in mice or humans with type 2 diabetes or those presenting with obesity [81–83]. These bacteria are known to synthesize short-chain fatty acids (SCFAs), which are known for their roles in the regulation of glucose and insulin levels, probably through inhibition of lipolysis in the hepatocytes, skeletal muscle, and adipose tissue [84]. SCFAs may also function by triggering anti-inflammatory Treg cells or by lowering cytokine levels [85]. Increased quantities of SCFA-producing bacteria offer a beneficial effect in protecting the offspring against HFD-induced metabolic dysfunction [70]. This study suggests that natural products may not only act via the modulation of gene expression but also by restoring balance in the gut microbial composition of diet-induced animal models of MetS, athough, the mechanism by which this occurs has not been fully established.

Phytochemicals such as phytosterol, OA, ursolic acid (UA), and genistein have also proven effective in lowering serum or hepatic triglyceride (TG) levels and/or LDL-C levels, or increasing the levels of HDL-C, hence preventing dyslipidemia [15, 69–71]. A group of researchers [16] reported a marked decrease in the serum, liver, and muscle TG levels, including serum cholesterol and free fatty acid (FFA) of adult male offspring of green tea extract (GTE) supplemented HFD-fed dams. Consistent with these findings, grape skin extract (GSE) was effective at reducing plasma TG levels in adult offspring [17]. Although these studies did not investigate the detailed mechanisms of action by which these extracts or phytochemicals prevented the development of dyslipidemia in adult offspring, they did, however, established lipid-lowering effects in maternal or neonatal HF- or HFD-induced animal models. Further studies are therefore warranted to delineate the possible mechanism of the lipid-lowering effects of phytochemicals and plant extracts.

Phytosterol administration in hamster dams resulted in a 71% reduction in total cholesterol in the offspring. Similarly, significant decreases of 81, 50, and 36% in non-HDL-C, HDL-C, and TG levels were observed, respectively, in the progeny of high-cholesterol-fed dams [71]. Based on this analysis, phytosterol administration appears to cause a drop in HDL-C levels, however, this level is still within an acceptable range. Dietary intake of GTE by rat dams has also been shown to reduce offspring serum TG levels in adulthood from 122.9 mg/dL in the HFD controls to 88.8 mg/dL at 7.5 g/kg GTE and 78.7 mg/dL at 10 g/kg GTE [16]. Two studies on genistein reported its beneficial health effects. One of the studies investigated the influence of genistein on some features of MetS [70], while the other focused on its effect on NAFLD [86]. In the study by Zhou et al. [70], no significant changes were observed in the serum levels of total cholesterol, LDL-C, and FFA in the offspring as a result of maternal genistein intake. It was however established that genistein administration in dams increased offspring HDL-C levels by 7.8%. Although Huang et al. [86] reported a downregulated expression of lipogenic genes, the serum lipid profile was not accounted for but instead showed that genistein prevented hepatic lipid accumulation in the offspring.

Oral administration of 60 mg/kg OA to female neonatal rats challenged with a double hit of an HF diet reduced plasma TG and cholesterol levels by 40 and 20%, respectively [15]. However, the plasma lipid profiles of their male counterparts were not significantly different. A higher dose of OA might have produced a statistically significant change in the plasma lipid profile of the male rats. Although the authors assayed the total concentration of cholesterol across the various treatment groups in their work, they, however, did not consider the concentrations of its different subtypes, unlike the studies conducted on phytosterol and genistein as discussed above. Neonatal administration of UA was reported to have no significant impact on plasma TG and cholesterol levels of HF-fed rats [87].

In another study, HS aqueous extract had sex-specific actions in rats. In males, it reduced cholesterol level by 19% while in females, it lowered TG levels by 13% [72]. Similarly, maternal consumption of GSE in rats prevented a rise in TG levels in 90- and 180-day-old offspring, however, it had no significant effect on total cholesterol levels [17]. On the contrary, in a low-birth-weight and HF diet-induced model of metabolic dysfunction, a citrulline supplement given to neonates of protein-restricted dams increased liver TG content and lowered the hepatic cholesterol level, but did not alter plasma TG and HDL as well as glucose metabolism at post-natal day 90 in rats [88]. This can be explained in part by the action of citrulline in the upregulation of *Fas* and *Srebp1*, which promotes lipogenesis, as reported in this study. Conversely, previous studies in a curative approach suggested that citrulline downregulates *Srebp1* [89] and prevents hypertriglyceridemia induced by HF intake [90]. Of course, a number of factors may account for the disparity in observations in response to citrulline supplementation. A lower dose of fructose (10%) for 8 weeks adopted by Tran et al. [88] compared to a higher dose of fructose (60%) for 8 weeks [89] is not likely to be responsible for increased hepatic TG levels in response to citrulline supplement as reported by Tran et al. [88]. The dosage and duration of both studies are also far apart. So, a higher dose of citrulline (2 g/kg) adopted by Tran et al. [88] compared to 0.15–1 g/kg used in previous studies [89, 90] may have contributed to the discrepancies in these studies. This suggests that citrulline at a higher dose may negatively impact TG metabolism.

Based on the available evidence, an insight into both the molecular mechanism and gut bacteria-associated activity of natural products would enable a proper grasp of their ability to program against MetS. In addition, harmonizing the doses of plant extracts and phytochemicals in experimental studies, with very minimal variation in experimental design, is crucial to making reasonable comparisons between different studies and would help improve our understanding of their roles and mechanism of action.

Insulin resistance and glucose metabolism

Insulin resistance is a condition characterized by an inability of insulin to act on target tissues [91]. In this condition, insulin is present at a normal concentration, but the tissues are unresponsive to its stimulation and as a result, more insulin is secreted, thereby leaving fasting plasma insulin at high levels [92, 93]. It usually results from a disrupted metabolism. Insulin resistance is a component of MetS and a risk factor for cardio-metabolic disorders [94].

With respect to insulin resistance, certain phytochemicals and plant extracts have demonstrated a protective effect (▶ **Table 1**). Some plant extracts and phytochemicals have been shown to lower insulin resistance, thereby improving insulin action on target tissues. The resultant effect is the normalization of blood glucose levels, although some studies reported that some of these phytochemicals or plant extracts exert no significant effect on glucose levels and insulin sensitivity [72, 88]. Two studies on GTE have given conflicting reports on the glucose profile and insulin sensitivity [16, 69]. Decreases in the serum insulin level and insulin resistance index were observed in offspring of high-fat-fed dams supplemented with GTE compared to those fed an HFD only [16]. GTE was shown to affect serum glucose levels in a dose-dependent manner, where 10 g/kg of GTE lowered the blood glucose concentration, but a dose of 7.5 g/kg produced no significant change in the glucose levels. Additionally, the same study recorded that post-weaning intake of GTE in rats born to high-fat-fed dams did not result in a decrease in insulin and the insulin resistance index value [16]. This constitutes yet another evidence of metabolic programming, which suggests that GTE acted during pregnancy or lactation or both to bring about its effect.

Also, maternal GTE consumption lowered basal glucose levels but had no effect on the HFD-induced increase in insulin levels in rat offspring [69]. Interestingly, both studies on GTE reported its beneficial effect in reducing serum cholesterol levels. The discrepancy in the effect of GTE on glucose metabolism in these studies may be dose related as the dose adopted by Li et al. [16] was higher than that used by Hachul et al. [69], even though both had a similar duration of intervention.

Improved insulin sensitivity was also observed in HFD-fed adult offspring following maternal resveratrol supplementation (200 mg/kg) during pregnancy and lactation as indicated by enhanced glucose tolerance. However, resveratrol did not lower glucose levels in the HFD-fed mice offspring [14]. Consistent with this finding, maternal quercetin administration enhanced glucose metabolism and insulin sensitivity in adult offspring of obese dams [95]. However, a contrary observation was made by Ros et al. [96], who demonstrated an increased glycemic level in pups following maternal resveratrol supplementation in HFD-fed dams (2.5 mg/kg). The disparity in the findings may be partly explained by the difference in the experimental design. Zou et al. [14] administered a high dose of resveratrol and subjected the dams to 11 weeks of HFD, while Ros et al. [96] fed the dams a very low dose of resveratrol and euthanized the pups and dams immediately after the suckling period was over. Oral administration of OA in neonatal rats demonstrated a remarkable degree of protection from the adverse effects of HF consumption in adulthood. At 60 mg/kg, OA for 7 days normalized fasting blood glucose and homeostatic model assessment of insulin resistance (HOMA-IR) in adulthood [15]. OA offered significant protection against the development of insulin resistance via the upregulation of adiponectin levels by approximately 1.5-fold. Increased adiponectin levels in neonatal OA-administered rats are indicative of increased insulin sensitivity, hence, normalizing glucose levels compared to HFD-fed rats with lower levels of adiponectin [80]. The same observation was reported for maternal genistein intake on the offspring's glucose profile [70]. The progenies of genistein-supplemented dams experienced a pronounced improvement in the glucose profile. A significant reduction was observed in glycemic levels and insulin concentrations as well as HOMA-IR of the adult offspring [70].

Supplementation with GSE to lactating dams also supported the foregoing assertions regarding the benefits of these natural products on glucose homeostasis. At days 90 and 180, the study by Resende et al. [17] showed that while offspring of HFD-fed dams without supplementation developed considerable resistance to insulin, the reverse was the case for offspring from HFD-fed dams supplemented with 0.6 g/kg GSE. High-performance liquid chromatography analysis of the GSE identified four different anthocyanins as its major phytochemical composition responsible for the physiological activity [17]. S-allyl cysteine, administered during the neonatal period for 15 days in rats, did not alter insulin levels [97]. Another study by the same investigators reported that s-allyl-cysteine produced an insulinotropic effect immediately after the weaning period in the absence of a second hit of fructose insult [98], thus demonstrating a time-bound effect of s-allyl-cysteine. The time-bound effect could also explain the increased glucose levels observed in the offspring of HFD-fed dams upon weaning in response to resveratrol intake [96]. In separate studies, neonatal administration of UA [87] and HS extract [72] exhibited no prominent effect on the glucose profile and HOMA-IR. Collectively, these results show that plant extracts and phytochemicals may improve glucose metabolism by enhancing the sensitivity of target organs to insulin and the upregulation of adiponectin levels, hence abating HFD-induced hyperglycemia.

Body weight, fat mass, and adiposity

Increased body weight and adiposity are potential risk factors for the development of obesity. Since obesity is one of the principal predisposing factors for MetS, increased consumption of certain medicinal plants, fruits, vegetables, nuts, vegetable oils, and other rich sources of phytochemicals by expectant obese mothers could substantially minimize the vulnerability of their offspring to obesity in later life. Although limited studies are available to arrive at this conclusion, some animal studies, as reported in ▶ **Table 2**, have established improved body weight and adiposity of offspring

as well as overall metabolic activity following intervention by phytochemical or medicinal plant extracts in obese dams or neonates. Developmental events occurring in the neonatal period of altricial species such as rats and mice are equivalent to the events occurring in the third trimester of precocious species like humans [99]. Hence, neonatal studies in animals are translatable to the critical window of developmental plasticity in humans.

Phytochemicals that have exhibited a demonstrable impact in preventing a high-fructose or high-fat diet-induced increase in body weight include resveratrol, oleanolic acid, quercetin, and genistein [15, 70, 95, 96]. These phytochemicals were administered to pregnant or lactating dams and their effects were subsequently observed in the offspring. Alternatively, some of these phytochemicals were given during the neonatal period and their effects observed in later life after an HF or HFD challenge. On the contrary, curcumin, s-allyl cysteine, GTE, and HS have not been reported to cause any significant changes in body weight [69, 72, 97, 100].

Maternal resveratrol supplementation reduced the birth weight in offsprings of HFD-fed dams in mice [14]. A reduction was also observed in white adipose tissue (WAT) but not in brown adipose tissue (BAT) mass. Resveratrol was reported to stimulate increased energy expenditure in BAT of HFD-fed offspring via the activation of AMPKα and nicotinamide adenine dinucleotide-dependent deacetylase sirtuin-1 (SIRT1) [14]. Resveratrol also promoted thermogenesis by upregulating the expression of thermogenic genes (*Prdm16, Cidea, Elovl3* and *Pgc1α*, *p-Ampkα*, and *Sirt1*) in inguinal WAT and epididymal WAT in the offspring. Hence, by the mechanisms highlighted above, resveratrol protected against obesity in the offspring of obese dams fed a HFD post-weaning. A similar outcome was observed at weaning in a study by Ros et al. [96] in which body weight was significantly decreased in the offspring following resveratrol supplementation in the dams. Accordingly, resveratrol reduced adiposity in subcutaneous adipose tissue in male and female offspring and had a sex-dependent effect on visceral adipose tissue (VAT) [96]. However, resveratrol decreased VAT only in female offspring in the same study.

Furthermore, resveratrol was also found to prevent excessive fat accumulation by downregulating adiponectin and *fas*, though no significant change in SIRT1 levels was observed. OA administration in neonatal rats prevented weight gain in adulthood following a high-fructose insult [15, 101]. Oral administration of quercetin to rat dams during pregnancy and lactation prevented an HFD-induced increase in body weight in adult offspring [95]. The regulation of lipid metabolism at the level of transcription and increased energy expenditure in BAT and WAT is therefore a potential mechanism by which plant products program protection against obesity.

Hypertension

Adulthood hypertension can be programmed in response to a suboptimal environment in early life [102]. Blood pressure is primarily regulated by the kidneys. The developing kidney is vulnerable to early-life insults which may produce renal programming and programmed hypertension [103]. HFD intake, nitric oxide (NO) deficiency, and oxidative stress have been implicated in the developmental programming of hypertension [104, 105]. NO is a vasodilator. Asymmetric dimethylarginine (ADMA), an endogenous NO synthase inhibitor, plays a key role in the regulation of NO-reactive oxygen species (ROS) balance [106]. An imbalance between NO and ROS produces oxidative stress, which is involved in the development of programmed hypertension [105]. Resveratrol supplementation (50 mg/L in drinking water) to rat dams during pregnancy and lactation prevented hypertension via the restoration of NO bioavailability (increased L-arginine to ADMA ratio, increased NO_2^- levels) and reduction of oxidative stress in offspring of HDF plus bisphenol A induced hypertension in adulthood [107]. Similarly, supplementation of resveratrol during gestation and lactation in rats prevents hypertension by reducing oxidative stress and modulating gut microbial composition in offspring challenged with N-nitro-L-arginine-methyl ester treatment and an HFD in prenatal and postnatal periods, respectively [108].

Apart from resveratrol, two plant extracts have been reported to confer protection against programmed hypertension in different programming models [17, 109]. GSE prevented adulthood hypertension in offspring born to high-fat-fed rat dams [17]. *Euterpe oleracea* extract has been reported to prevent programmed hypertension in adult offspring of low-protein-fed dams [109]. These findings further support the use of some medicinal plants and phytochemicals to prevent adulthood hypertension of developmental origin.

Non-alcoholic fatty liver disease

A few studies have investigated the potential of plant products as prophylactic agents against NAFLD in the context of metabolic programming. This disease is characterized by pathological conditions such as hepatic steatosis, non-alcoholic steatohepatitis (NASH), and secondary complications such as hepatic fibrosis, which may eventually lead to cirrhosis and hepatocellular carcinoma if not properly managed [110]. NASH is associated with lipid peroxidation and production of free radicals that elicit inflammation and activate stellate cells in the liver, which collectively result in fibrosis [111, 112].

When neonatal Sprague-Dawley rats were administered 10 mg/kg of UA and fructose, followed by HF consumption in adulthood, fructose-induced hepatic lipid accretion was suppressed by UA compared to the control groups [87]. Similarly, 60 mg/kg of OA administered to suckling Sprague-Dawley rats counteracted the adverse effects of an HF diet by significantly decreasing the hepatic lipid load [101]. In HF-fed adult Sprague-Dawley rats of both sexes, curcumin, at 500 mg/kg body mass administered during suckling, conferred protection against NASH and lowered hepatic lipid accumulation in female, but not in the male, rats [100]. In another study, neonatal administration of genistein for 5 days post-natal protected against HFD-induced hepatic steatosis and NASH in adult rats [86]. Converging evidence has apparently demonstrated the potential of phytochemicals as prophylaxis against the development of NAFLD and, as such, may serve as a natural strategic intervention in abating NAFLD in the general populace.

Knowledge gaps and recommendations

This review provides an overview of the medicinal herbs and phytochemicals with potential for use as reprogramming agents to

offset developmentally programmed MetS. Even though attempts have been made to provide plausible explanations on how plant extracts and phytochemicals could prevent programmed MetS, there is little research about the interaction between these natural products and epigenetic marks in programming models. Epigenetic changes, given its importance in metabolic programming, should be investigated to further understand the mechanism of action of plants and phytochemicals in the prevention of programmed MetS. There is also a need to assess toxicity and evaluate safety doses of herbal medicines and phytochemicals in humans. On the same basis, robust clinical trials with the aim of developing natural product-enriched supplements to ascertain effective interventions during pregnancy and the early postnatal period for the prevention of MetS and other chronic diseases are urgently needed to juxtapose the claims from experimental animal studies.

Conclusions

Ample experimental evidence indicates that medicinal plants and phytochemicals confer a substantial degree of protection against developmentally programmed MetS. It can be deduced that the majority of these agents are potentially strong candidates for mitigating the incidence of MetS and related NAFLD. Given their unparalleled health benefits and negligible side effects, medicinal plants and phytochemicals are on the path to transforming protective reprogramming against the development of MetS in individuals exposed to suboptimal conditions in the fetal and neonatal periods.

Contributors' Statement

Conceptual framework: K. G. I. and K. A. A.; scientific assessment and approval of review proposal: M. U. I., M. B. A. M. B. B., I. M., and B. A.; drafting the manuscript: K. A. A., K. G. I., I. M., M. B. B., B. A., and M. U. I.; concept and preparation of figure: K. A. A., K. G. I., and I. M.; critical revision of the manuscript: M. B. A., M. U. I., I. M., M. B. B., and B. A. All authors read and agree on the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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