

Original Article

Effects of preharvest factors on antidiabetic potential of some foods and herbal plants

Efeitos de fatores de pré-colheita no potencial antidiabético de alguns alimentos e ervas

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Abstract

Diabetes is a metabolic disorder with no definite treatment, but it can be controlled by changing lifestyle and diet. Consumption of high-fiber and nutrient-rich foods including vegetables have been shown to reduce risks of obesity and Type II Diabetes Mellitus (T2DM). Also, many herbal plants have been associated with reduced risks of T2DM because of their composition of secondary metabolites. Antioxidant activities of some secondary metabolites have potent inhibitory effects against inflammation linked with insulin resistance and oxidative stress. More than 800 known medicinal plants are used to control diabetes and its relevant complications. However, variations in preharvest factors including plant genotype, growing medium properties, climatic factors, and management practices can influence plant growth and their accumulation of phytochemicals with health-promoting properties. However, the effects of these preharvest factors on the antidiabetic properties of plant secondary metabolites are neither explicit nor easily accessible in the literature. Therefore, this review aims to document recent studies that reported on under-exploited medicinal plants with antidiabetic properties. We reviewed several important preharvest factors that can potentially affect the synthesis of phytoconstituents which possess antidiabetic properties. This review will help identify gaps for future research in phytomedicine and functional foods.

Keywords: antidiabetic, secondary metabolites, medicinal plants, natural amendment, LED light.

Resumo

O diabetes é um distúrbio metabólico sem tratamento definido, todavia pode ser controlado a partir de mudanças no estilo de vida e na alimentação. O consumo de alimentos ricos em fibras e nutrientes, incluindo vegetais, demonstrou reduzir os riscos de obesidade e Diabetes Mellitus tipo II (DM2). Além disso, muitas plantas herbáceas têm sido associadas a riscos reduzidos de DM2 devido à sua composição de metabólitos secundários. As atividades antioxidantes de alguns metabólitos secundários têm efeitos potentes de inibição contra inflamações associadas à resistência à insulina e ao estresse oxidativo. Existem mais de 800 plantas medicinais conhecidas utilizadas no controle do diabetes e suas complicações. No entanto, variações nos fatores de pré-colheita, incluindo genótipo da planta, propriedades do meio de cultivo, fatores climáticos e práticas de manejo, podem influenciar em seu desenvolvimento e seu acúmulo de fotoquímicos com propriedades promotoras. Apesar disso, os efeitos desses fatores de pré-colheita nas propriedades antidiabéticas de metabólitos secundários de plantas não são explícitos nem facilmente acessáveis na literatura. Portanto, esta revisão tem como objetivo documentar estudos recentes que relataram plantas medicinais subexploradas com propriedades antidiabéticas. Revisamos diversos fatores pré-colheita importantes que podem afetar potencialmente a síntese de fitoconstituintes que possuem propriedades antidiabéticas. Assim, esta revisão auxiliará na identificação de lacunas para pesquisas futuras em fitomedicina e alimentos funcionais.

Palavras-chave: antidiabético, metabólitos secundários, plantas medicinais, correção natural, luz LED.

1. Introduction

Plant growth, development, phytochemical composition, and subsequent biological properties are determined by preharvest factors such as genotypic characteristics, growing media, atmospheric conditions, and agricultural management practices (Aftab, 2019). Preharvest factors

refer to many cultural practices or treatment methods applied to plants cultivated in indoor production systems or the farm before harvesting time that can influence quality and quantity of plant production. Regulating these preharvest parameters can be a practical strategy to

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increase the bioactive composition of high-quality crops as the growing population demands (Nguyen et al., 2019). In the last decade, previous researchers evaluated the impacts of preharvest factors on plant morphophysiological responses, phytochemicals, and pharmaceutical properties, particularly antioxidant and antidiabetic activities (Ullah et al., 2019).

Secondary metabolites are organic non-nutritional compounds synthesized by plants. They provide long-term advantages to plants such as defense against biotic and abiotic stress agents (Rosenthal and Berenbaum, 2012). Due to their defense roles in plants, secondary metabolites are exploited for various purposes in medicinal, nutritional, and cosmetic companies (Jensen et al., 2014). Secondary metabolites exert an extensive range of bioactive and physiological functions such as antioxidants, anti-inflammatory, antimicrobial, anticancer activities, and many others (Kholkhal et al., 2013). In the last decade, the use of alternative medicines and herbal plants (about 800 species) to treat diabetes has dramatically increased due to availability and low side effects (Zhang et al., 2017a; Arumugam et al., 2013).

Diabetes is a disorder of metabolism divided into three classes: Type I Diabetes Mellitus (T1DM), Type II Diabetes Mellitus (T2DM), and gestational diabetes mellitus. The causes and complications of T2DM can be effectively managed, compared to T1DM and gestational diabetes mellitus. Obesity is one of the main causes of T2DM because excess fat contributes significantly to insulin resistance by lipid accumulation in the liver and releases increased amounts of pro-inflammatory cytokines, free fatty acids, glycerol, and hormones that have a vital role in developing insulin resistance. Then, insulin resistance, linked to pancreatic β -cells dysfunction, causes an increase in blood sugar concentration (Saad et al., 2017; Hardy et al., 2012). From the research of Bahmani et al. (2014), T2DM can be controlled by healthy lifestyles and diet choices. For instance, high-fiber and nutrient-rich foods (e.g., vegetables, legumes, and fruits) have been proved by research to help reduce risks of obesity and diabetes. Also, the use of medicinal plants is another effective approach to control T2DM because of their phytochemical composites including phenolics, flavonoids, anthocyanins, carotenoids, terpenoids, and many more (Bahmani et al., 2014). Antioxidant activities of some of these secondary metabolites illustrate potent inhibitory effects against inflammation that leads to insulin resistance and oxidative stress correlated with diabetes (Jung et al., 2014). Therefore, the purpose of this review is to document recent studies on under-exploited medicinal plants with antidiabetic properties. We reviewed how changing preharvest factors affects the synthesis of plant secondary metabolites that possess antidiabetic properties.

2. Preharvest Factors

Managing preharvest parameters is an effective and practical strategy to provide the health needs of the global population through producing high-quality food crops with enhanced bioactive compounds (Nguyen et al., 2019).

Preharvest factors include: 1) genotypic characteristics of the plant; 2) growing medium factors and amendments; 3) environmental factors like light quality, intensity, humidity, and temperature; 4) management practices such as planting and harvest time, irrigation, and fertilization. These factors influence plant growth and development, the composition, and the functional properties of phytochemicals (Aftab, 2019; Nguyen et al., 2019). Improving the yield of phytochemicals and their functional properties such as antioxidant and antidiabetic activities by controlling preharvest factors under greenhouse conditions have widely been reported by many researchers in the last decade (Ullah et al., 2019). Kaur et al. (2021) demonstrated that preharvest factors including growth stage and different plant parts significantly influence antioxidant and antidiabetic function in *Swertia chirata* Buch. For instance, it was shown that the DPPH activity was considerably higher in the leaves of *Swertia chirata* harvested at the bud stage compared to leaves harvested at the flowering stage by 4% at a concentration of 80 $\mu\text{g mL}^{-1}$ plant extraction. A similar observation was obtained for antidiabetic activity. The highest in-vitro α -amylase inhibitory activity in leaves harvested at the bud stage was higher by 3% compared to the flowering stage. Description of some of these important preharvest factors is further detailed in this review.

2.1. Growing media

Growing media are materials used to grow plants, and are categorized as soil (i.e., silty, sandy, clayey, and loamy soils) or soilless (i.e., pumice, calcine clay, perlite, peat moss, organic amendments, and wood-based substrates) (Gruda, 2011). Variations in the growing medium characteristics affect plant morphology, productivity, and phytochemical composition (Turhan et al., 2007). For example, Tabatabaei (2008) study reported that photosynthesis rate, growth, development, and contents of bioactive compounds were associated with optimum levels of growing medium aeration and balanced nutrients. The effects of natural amendments and types of soils on plant morpho-physiology and development, bioactive compounds, and medicinal activities are explained further below.

2.1.1. Soil bio-physicochemical properties

Soil is a dynamic substance consisting of mineral particles, water, gases, and organic matter. Texture, structure, and porosity are known as the physical properties of soil. These physical properties play a key role in soil quality and soil condition (Maddela et al., 2017). Soil texture contains the relative quantities of three mineral particles including sand, silt, and clay, which have a profound impact on many other properties such as the transpiration and exchange of gases in distinct soil layers. The soil texture classification to clay, loam, and sandy loam is based on particle size (Malique et al., 2019). Phogat et al. (2015) explained that soil types and structure affect plant growth components, improving aeration, nutrients and water availability, root penetration, and microbial activity. Different soil types possess various properties including different pH, moisture levels, and organic carbon percentage

which were shown to have noticeable effects on growth parameters and accumulation of antidiabetic compounds such as polyphenols and vitamin E in *Calotropis gigantea* (Kumari et al., 2018). Soil structures define a soil's density, which has a subsequent effect on morpho-physiological response such as seedling emergence, root penetration, oxygen supply, and

respiration (Stack, 2016). Tomato (*Solanum Lycopersicon*) growth parameters were significantly promoted with sandy soil modified with vermicompost (VC), in comparison with clay and silt loam soils amended with VC (Zucco et al., 2015). In addition, physicochemical properties of soils not only affect microbial diversity and their action but also influence microbial mass levels (Hassan and El-Kamali, 2015). Muscolo et al. (2019) illustrated that soil biochemical properties directly affect the biosynthesis of carotenoids and glucosinolates, and the antioxidant potential of *Brassica rpestris* Raf. Soil microbes including bacteria and fungi are involved in the biochemical processes within soils, and they are imperative to retain soil productivity and fertility. According to Radušienė et al. (2019), plant growth and development, and phytochemical concentrations are significantly influenced by soil fertility. Reduction in a diversity of soil microbes has been stated to have adverse outcomes on soil health and soil quality (Giller et al., 1997), which can considerably influence the biosynthesis of plant-based chemical compounds as reported in *Stevia rebaudiana* by Pal et al. (2015). Ortíz-Castro et al. (2009) explained that some soil microbes produce phytohormones and volatile compounds like auxins, cytokinins, gibberellins, and antibiotics that directly or indirectly influence plant growth and development. Besides, soil microbes also have a vital role in the recycling of major soil mineral elements such as carbon, nitrogen, phosphorus, and other elements that help maintain soil health and productivity (Aislabie et al., 2013). Soil microbes significantly contribute to decaying organic matter and transforming organic nutrients into their plant-available inorganic forms, a process known as mineralization. For instance, soil microbes were shown to have an essential role in the nitrogen cycle, providing inorganic forms of nitrogen like ammonium and nitrate for plants (Aislabie et al., 2013). Montoya-García et al. (2018) also mentioned that mineral constituents have a major effect on the primary metabolism and biosynthesis of bioactive compounds such as alkaloids, terpenoids, and phenolic compounds, which in turn affect plant growth and development. Pathak et al. (2008) clarified that nitrogen is vital in primary metabolism (i.e., the biosynthesis of nucleic acids, different amino acids, lipids, and enzymes). A study involving three medicinal plants (i.e., *Eucomos autumnalis*, *Tulbaghia ludwigiana*, and *Tulbaghia violaces*) showed that application of nitrogen, phosphorus, and potassium fertilizers or their deficiencies affected plant growth parameters, phytochemical production, and antioxidant activities (Aremu et al., 2014).

2.1.2. Natural amendments

Natural amendments consist of organic and inorganic but natural materials added to soil indirectly contribute to plant growth and development by enhancing soil fertility

and/or soil structure and conditions (Abbott et al., 2018). Natural growing amendments including compost, compost derivatives, vermicast, potassium humate, and manures provide potential benefits for the environment including 1) adding nutrients into the soil; 2) attracting earthworms; 3) supporting and protecting beneficial microbes; 4) promoting water retention capacity and release; and 5) enhancing nutrient absorption capacity and availability (Duong et al., 2012). Liu et al. (2016) observed that the application of carbon-rich natural fertilizers positively affected the biodiversity of soil, leading to the soil that is more resistant to pathogenic infections and environmental stress. Also, Lazcano and Domínguez (2011) earlier confirmed that the growth, yield, and phytochemical concentrations of different plant species can potentially be influenced and accelerated by applying various kinds of natural amendments. The positive results of growing medium amendments on plant growth are most likely connected to the optimum supply of essential macro and micronutrients required for growth and development, as well as the enhancement of soil functional activities. Celestina et al. (2019) claimed that the physicochemical features of soil have a vital impact on crop yield and these factors can be altered by applying various organic amendments.

Additionally, Lal (2006) confirmed that the administration of natural amendments effectively promotes crop production due to the amelioration of soil properties. Multiple scientific studies presented the effects of different amendments on phytochemicals accumulation and various biological activities like antioxidant properties. In the work by Antonious et al. (2014), they noticed that the use of natural amendments like chicken manure did not only affect the growth of two species of kale (*Brassica oleracea* cv. Winterbar) and collard (*Brassica oleracea* cv. Top Bunch) but significantly boosted the total content of phenols and ascorbic acid. Moreover, growth factors and accumulation of total phenolics, carotenoid, and carvacrol compounds in *Plectranthus* spp. were promoted by natural amendments. However, various organic amendments including vermicast, K-humate, and NPK indicated different effects on plant growth and phytochemicals in *Plectranthus* spp (Zhang et al., 2017a). Moreover, soil fertility and the production of essential oils in basil (*Ocimum basilicum*) were promoted in soils amended with vermicompost (Trivedi et al., 2017). Also, growth parameters, phenolic compounds' content, and kale's antioxidant properties (*Brassica oleracea* var. acephala) were differentially affected by different natural amendments such as dry vermicast, K-humate, and volcanic minerals (Iheshiulo et al., 2017).

Another important preharvest factor affecting plants' phytochemistry is growing media chemical composition. In the last decade, the use of alternative medicines and herbal plants has dramatically increased in synchrony with consumers' demand for organic produce. As a result, current researchers are focusing on applying natural amendments to enhance phytomedicines and the development of functional plants (Nguyen et al., 2019; Abbey et al., 2018). Research by Abbey et al. (2018) revealed that essential fatty acids, and mineral nutrients as well as antioxidant activities in kale (*Brassica oleracea* var. acephala) were

differentially altered by different natural growing medium amendments like dry vermicast, potassium (K)-humate, and volcanic minerals. Their results illustrated that dry vermicast had stimulatory effects on polyunsaturated fatty acid (PUFA) biosynthesis and monounsaturated glycolipids phosphatidylglycerol by regulating the monounsaturated molecular species metabolism. Also, it was shown that vermicast had a remarkable influence on the accumulation of oleic acid and omega-3 fatty acid compared to potassium (K)-humate, and volcanic minerals, which as a result increases the overall nutritional value and therapeutic properties of kale. In the findings obtained by Vidal et al. (2018), where the accumulation of essential lipids in kale (*Brassica oleracea* var. *acephala*) including total C18:1n9, C16:3n3, and C18:3n3 fatty acids were enhanced under the application of dry vermicast. It appeared that the positive effect of vermicast on functional lipids was closely associated with the enhanced potential activity of delta 13 desaturase enzyme that accelerated desaturation of C16:2n6 into C16:3n3. Additionally, the high N and other essential elements in vermicast contributed to the improved biosynthesis of C18:1n9 and C16:3n3 fatty acids in the kale. Collectively, the results obtained from both Abbey et al. (2018) and Vidal et al. (2018) presented promising and cost-effective approaches to enhancing functional lipids accumulation by applying natural growing media, in particular vermicast. The health benefits of these essential lipids on human physiology and reduced susceptibility and debilitating disease risks such as obesity, diabetes, and cancer has been widely reported (Nguyen et al., 2019).

2.2. Climatic factors

Climatic conditions including light, temperature, humidity, salinity, drought, and other environmental factors have either stimulatory or inhibitory effects on plant growth and development and their biosynthesis of chemical compounds (Schreiner et al., 2012). Ghasemi et al. (2011) acknowledged that climatic factors cause major differences in the accumulation of plant secondary metabolites and biological activities, as further discussed in this review. As Dong et al. (2011) confirmed, temperature and light regimes significantly influenced the accumulation of phytonutrients in *Eucommia ulmoides*. Nevertheless, it should be highlighted that majority of the literature available on how climatic factors impact the antidiabetic potential of food crops and medicinal plants are very scanty, compared to their antioxidative effects.

2.2.1. LED light treatments

Light quality, intensity, and duration have potential effects on seed germination, plant growth, photosynthesis, flowering, and the accumulation of secondary metabolites (Montgomery, 2016). According to Metallo et al. (2018), various metabolic pathways can be influenced by lighting. Transcription factors and photoreceptors can significantly control cellular division, endoreplication, and cell growth which are directly affected by different qualities, durations, and intensities of light (Okello et al., 2016). Huché-Théliér et al. (2016) indicated that ultra-violet (UV) and blue (B) lights have considerable roles in controlling

and regulating an extensive range of metabolic processes in pepper (*Capsicum annum*), lettuce (*Lactuca sativa*), cucumber (*Cucumis sativus*), *Arabidopsis*, and tomato (*Solanum Lycopersicon*). Thus, the manipulative use of blue and UV-B lights can help improve plant growth and development, and resistance versus pests and pathogenic diseases for increased nutritional and phytochemicals values (Abidi et al., 2013). Ullah et al. (2019) observed secondary metabolites and activating defense mechanisms similarly. Hou et al. (2010) investigated the relationship between low light intensity and growth indices as well as phytochemical compounds in *Glycyrrhiza uralensis* Fisch. According to these researchers, although low light intensity negatively impacted leaf thickness, photosynthesis, plant growth, and productivity, it noticeably promoted chlorophyll and phytochemical contents such as glycyrrhizic acid and liquiritin that can be associated with the stimulatory effects of low light intensity on phytochemical biosynthesis and reduced plant biomass production. These findings disagreed with the work by Neugart et al. (2016) who found that flavonol concentration including quercetin glycosides, a caffeic acid monoacylated kaempferol triglycoside, and disinapoyl-gentiobiose of kale leaf tissue was higher in plants exposed to higher light intensity ($400 \mu\text{mol m}^{-2} \text{s}^{-1}$) compared to lower light intensity ($100 \mu\text{mol m}^{-2} \text{s}^{-1}$). It was found that the differences flavonoid content in plants treated under different light intensity was associated with the effect of light intensity on R2R3 MYB transcription factors required in the phenylpropanoid pathway as well as the expression of genes involved in coding protein degradation, transport processes, amino acid biosynthesis, and different secondary pathways. Moreover, the regulatory effect of light intensity in the expression of genes involved in the flavonoid biosynthetic pathway that enhance flavonoids and hydroxycinnamic acid derivatives accumulation can be linked to anti-photo-oxidative and ROS scavenging mechanisms caused by excess light intensity, had been reported in previous studies. In another study, phytochemical biosynthesis such as phenolics, tocopherols, flavonoids, and glucosinolates in *Ananas comosus* L. was significantly enhanced by the application of UV radiation between 190-280 nm (Freitas et al., 2015). Arakawa et al. (2017) illustrated a potent relationship between different blue light wavelengths (430 to 490 nm) and the accumulation of anthocyanin compounds in *Prunus avium* L. From their work, the wavelength 450 nm (blue light) was found to be more effective at stimulating anthocyanin synthesis as compared to other wavelengths. In agreement with the findings of Eckstein et al. (2012), plants exposed to higher ratio of blue light had an elevated level of soluble carbohydrates such as sucrose, glucose, and fructose. Such as this enhanced plant metabolism and detoxification pathways as well as amino acids, and lipids biosynthesis in response to ROS induced by stressful blue LED treatments. Nishimura et al. (2007) reported that the plant growth parameters and chemical composition of *Hypericum perforatum* L. can be changed by applying various light qualities including blue, white, and red lights at different intensities. They found the highest rate of growth under white and red-light treatments with $500 \mu\text{mol m}^{-2} \text{s}^{-1}$ intensity while the highest content of

phytochemicals such as hypericin and pseudohypericin are anthraquinone derivatives, which possess anti-cancer and anti-inflammatory properties, was obtained by the used of red-light with $250 \mu\text{mol m}^{-2} \text{s}^{-1}$ intensity. In agreement with this study is the results of Metallo et al. (2018), where the combination of blue and red as well as white LED light treatments significantly influenced yield, morphological characteristics, beneficial nutrients, and phytochemicals in *B. oleracea*. Based on the results, the highest total concentrations of carotenoid and glucosinolates observed with 37 days of white LED treatment and 5% blue/95% red LED may be related to the differences in growth and development stage and cultivar. Moreover, Ali and Abbasi (2014) reported notable effects of light treatments including 24, 27, 30, and 37 days with $40 \mu\text{mol m}^{-2} \text{s}^{-1}$ intensity on plant morphology and phytochemical production as well as antioxidant potential in *Artemisia absinthium*. Based on their results, the light showed a stimulatory and positive effect on phenolic compound accumulation and antioxidant activities. The highest level of total phenolic compounds (i.e., 42.96 mg/L) was obtained by applying continuous light treatment for 27 days. Liu (2013) stated that a purposeful manipulation of light quality and intensity to improve the accumulation of secondary metabolites and their bioactive properties enhanced the nutritional value of plants and pharmaceutical activities. Moreover, Bantis et al. (2016) demonstrated that variable LEDs meaningfully influence growth parameters and the total phenolic content of two *Ocimum basilicum* cultivars. An elevated level of phenolic compounds was observed under the combination of 1% UV + 20% blue + 39% green + 35% red + 5% far-red LED light spectra at $200 \mu\text{mol m}^{-2} \text{s}^{-1}$ intensity. It may connect to the stimulatory effect of blue light on the function of phenylalanine ammonia-lyase (an important enzyme in the phenylpropanoid biosynthetic pathway) which resulted in improving phenolic production. The effect of monochromatic B LED light, as physical stress elicitation, on the enhanced expression of a gene involved in phenylalanine ammonia-lyase activity and antioxidant potential in red leaf lettuce (*Lactuca sativa*) was already reported by Son and Oh (2015). Based on the results obtained by Hunaefi et al. (2018), combined ultraviolet (UV) and ultrasonic treatments (US) showed a positive potential effect on stimulation of targeted phenolic compounds like rosmarinic acid (RA) and enhanced antidiabetic activity of *Orthosiphon aristatus*. It was shown that the US and UV treatment increased the activities of the pentose phosphate pathway (G6PDH) and the phenylpropanoid pathway (PAL) enzymes; thereby providing precursors for the phenolic compounds' synthesis. The authors also reported that the combination of UV and US effectively increased the potential activities of α -glucosidase and α -amylase enzymes. These enzymes have prominent effects on the control of hyperglycemia related to type II diabetes. Consequently, this can be connected to the presence of higher phytochemical concentration, which led to the highest antioxidant function in vitro shoot cultures of *Orthosiphon aristatus*. However, more investigation should be conducted regarding interactions between supplemental light treatments and other growing conditions including temperature and various organic amendments towards

the enhancement of plant secondary metabolites and their antioxidant and antidiabetic properties.

2.2.2. Temperature

Temperature is known as one of the main abiotic stresses that control morpho-physiological components, productivity, and accumulation of phytochemicals in plant species. The optimum range of temperature (20° - 30°C) stimulates and increases several important chemical antioxidants and enzymatic antioxidants (i.e., superoxide dismutase, and catalase) (Zobayed et al., 2005). Ncube et al. (2012) explained that several plant physiological, biochemical, and molecular alterations are closely linked to temperature stress and as a result, these changes can influence phytochemical production. For instance, high temperatures ($>33^{\circ}\text{C}$) were shown to have an inhibitory effect on growth response, development, productivity, phytochemical content, and physiological activities (i.e., germination and photosynthesis) in *Phaseolus vulgaris* and *Vitis vinifera* (Hasanuzzaman et al., 2013). The molecular assessment results showed a strong correlation between heat stress and increment in ion transporters and signaling molecules. Nitric oxide and calcium ion, proteins such as cytosolic heat shock proteins (HSPs) and heat stress-associated 32-KD protein (HSA32), osmo-protectants, and antioxidants as well as other factors involving in signaling cascades and transcriptional regulation mitigated the adverse effects of high temperature in plant morphophysiological which caused enhanced phytochemical responses (Hasanuzzaman et al., 2013; Krasensky and Jonak, 2012).

Implementing various ranges of temperatures i.e., $20/12^{\circ}\text{C}$, $25/17^{\circ}\text{C}$, $30/22^{\circ}\text{C}$, $35/27^{\circ}\text{C}$, and $40/32^{\circ}\text{C}$ daytime and nighttime respectively, significantly affected seed germination, seedling emergence, growth, and developmental responses in Cotton (*Gossypium hirsutum* L.) (Reddy et al., 2017). Reddy et al. (2017) found a linear and positive relationship between increasing temperatures and improvement of physiological and morphological parameters, with the optimum treatment being a $35/27^{\circ}\text{C}$ (day/night) temperature regime. Similarly, temperature variations affected the composition of phytochemical compounds in *Brassica oleracea* as observed by Neugart et al. (2016). Their findings demonstrated that the hydroxycinnamic acid derivative content like disinnapoyl-gentiobiose was enhanced at higher temperature treatment (1.65 mg/g of dry weight at 15°C), while sinapic acid acylated flavonol tetraglycosides like kaempferol-3-O-sinapoyl-sophoroside-7-O-diglucoside was promoted at lower temperature (2.34 mg/g of dry weight at 5°C). The findings obtained from the molecular-level evaluation showed that temperature factors differentially affected the overall expression of genes involved in phenylpropanoid secondary metabolism. the biosynthesis of aromatic amino acids is a prerequisite of phenolic compounds production and phytohormone synthesis. Also, the results indicated that few more genes were expressed at low temperatures in contrast to high temperatures that may induce genes that are linked to the enrichment of jasmonate hormone metabolism to acclimate lower temperature and reduce

cold stress. Furthermore, the highest antioxidant function was observed in kale species exposed to lower temperatures (i.e., 3.8°C compared to 9.7°C) due to the presence of higher levels of flavonoid glycosides derivatives including quercetin-3-O-hydroxyferuloyl-sophoroside-7-O-D-glucoside (2.54 mmol GAE g⁻¹ of dry matter) and quercetin-3-O-disinapoyl-triglucoside-7-O-D-glucoside (4.19 mmol GAE g⁻¹ of dry matter), which enhance ROS-scavenging activity. Also, biosynthesis of phenylalanine ammonia-lyase and chalcone synthase enzymes involved in the biosynthesis of flavonoid pathway were noticeably increased under lower temperature, resulting in enhanced phenolic compounds production, as reported by Zietz et al. (2010). Odabas et al. (2010) examined the interaction effects of temperature variations on the metabolic profile of *Hypericum perforatum* L. They observed a strong correlation between temperature and light intensity on the biosynthesis of phenolic and polyphenolic accumulations including amentoflavone, apigenin-7-glucoside, chlorogenic acid, hyperoside, kaempferol, quercetin and quercitrin. The significance of temperature (from 24°C to 32°C) and light intensity (803.4 μmol m⁻² s⁻¹ to 1618.6 μmol m⁻² s⁻¹) increments on enhancement of phenolic compounds may be explained by alterations in photosynthetic activity, resulting in increased carbon availability unusually used for phytochemical synthesis in response during stress. Also, these physiological changes induced by these physical stress elicitation can be linked to increases in secondary metabolites to strengthen defensive systems. Zhang et al. (2009d) also observed the highest level of the terpenoid geosmin in *Lyngbya kuetzingii* at low temperature (10 °C) and low light intensity (10 μmol m⁻² s⁻¹) for 14 days. However, the content of geosmin production remarkably declined when the plant was subjected to high temperatures (25 and 35 °C) and high light intensities (20 and 75 μmol m⁻² s⁻¹). The effects of these external environmental stimuli on molecular mechanisms involved in geosmin production have been attributed to the biosynthesis pathway of geosmin. However, Khan et al. (2011) explained that these changes in environmental factors led to the production of phenolics, flavonoids, and alkaloids compounds, which have a key role in the defense mechanisms of plants exposed to temperature stress. According to Sarıkamış and Çakır (2012), the application of low-temperature treatments (0 °C at two-time durations (1 h) and (2 h) showed an inhibitory effect on the production of glucosinolate constituents and biological activities in broccoli (*Brassica oleracea* var. *Italica* L.). Glucosinolates are accumulated in plant cell vacuoles that lie adjacent to myrosin cells full of myrosinase enzyme, which is responsible for the hydrolysis of glucosinolates. The reduction in glucosinolate production may relate to the adverse effect of lower temperature on cellular integrity and subsequent interaction between myrosinase and glucosinolates, resulting in hydrolyzing and breaking down of glucosinolates. However, Pennycooke et al. (2005) revealed that low-temperature treatments (-5 °C) considerably increased the accumulation of anthocyanin compounds in *Petunia* (*Petunia* × *hybrida*) that may connect to the activation of antioxidant defense systems due to the presence of oxidative damage and lipid peroxidation induced by cold treatments. Nevertheless, the

productivity, quality of bioactive compounds, essential oils, and antioxidative capacity in three medicinal plants (i.e., *Nepeta cataria* L., *Melissa officinalis* L., and *Salvia officinalis* L.) were significantly influenced under the amplitudes of 15-20-25 °C temperatures. Although the maximum essential oils yield in *Melissa officinalis* was obtained at 25 °C, the highest amount and quality of essential oil and yield in *Nepeta cataria* and *Salvia officinalis* were observed at 15 and 25 °C, respectively (Manukyan and Schnitzler, 2006).

Since the effects of various temperature treatments on medicinal properties, specifically, antidiabetic activity is understudied, more research projects should be carried out to clarify temperature effects on phytochemicals and their bioactive properties. Additionally, there is still a need to consider the interaction between temperature regimes and other environmental factors towards enhancing plant secondary metabolites and their pharmacological activities.

2.2.3. Humidity

Humidity is known as one of the important climatic agents that improve germination rate, growth, development, and photosynthesis by increasing stomatal conductance in plant species (Suzuki et al., 2015). As Deng et al. (2016) confirmed, there is a strong correlation between humidity and plant productivity, biomass, and growth factors in many plant species. In one study, the morphological and physiological characteristics of *Rosmarinus officinalis* were highly influenced by the manipulation of humidity under greenhouse conditions (Sánchez-Blanco et al., 2004). According to the results obtained by Fu et al. (2018), the total flavonoids, polyphenols content, and antioxidant properties were promoted in *Pericarpium Citri Reticulata* (*Citrus reticulata* 'Chachi') under low humidity (50%) compared to high humidity (80%). The authors reported positive relationship between lower humidity and enhanced plant phytochemicals through control and improved internal chemical reactions. Water unavailability at lower humidity led to regulating enzymatic and chemical reactions plus decreasing non-enzymatic browning reactivity. It was explained by Zhang et al. (2015c) that non-enzymatic browning link to phenolic decomposition or changes of their chemical structure, which in turn increase decarboxylation and polymerization of phenolics, resulting in a reduction in antioxidant potential. In agreement are the results Kim et al. (2015b) obtained, where ascorbic acid accumulation enhanced from 10 to 84 ppm, and its antioxidant potential was significantly promoted in corn (*Zea mays*) at low humidity. Likewise, Kim et al. (2015a) confirmed that the accumulation of α-tocopherol and antioxidant potential was reduced in corn by increasing relative humidity. In a similar work carried out by Shin et al. (2007), although phenolic concentrations were significantly enhanced in strawberry (*Fragaria* × *ananassa* Duch.) at 75 and 85%, ascorbic acid concentration was decreased due to increased oxidation at lower humidity. While total flavonoids were increased at 95% humidity, anthocyanin concentrations and antioxidant activities were relatively unchanged at different relative humidity.

The effects of various relative humidity on growth factors, phytochemicals, and medicinal properties,

particularly antidiabetic activity, has not been extensively studied. Future research should be conducted to elucidate humidity effects on different aspects of plant morpho-physiological components, phytochemical content, and pharmaceutical properties.

2.3. Agricultural management practices

Agricultural management practices (AMPs) are beneficial and cost-effective activities associated with the application of production, economic, and management fundamentals (Bai et al., 2018). For example, AMPs present practical guidance regarding the management of fertilizers or manures to effectively restrain or decrease the movement of pollutants into the surface and groundwater as well as air (Sith et al., 2019; Merrill et al., 2011). Proper management practices considerably impact soil texture, fertility, nutrient concentration, moisture, and health status, which directly influence growth response, development, and plant biomass production (Rathore et al., 2011). Thus, contributing to sustainable plant production for food security via the supply of food crops enriched with high-value bioactive compounds (Móznér et al., 2012; García-Mier et al., 2013).

In this review, several important agricultural management practices including irrigation and fertilizer on plant growth aspects, the biosynthesis and concentration of phytochemicals, and medicinal activities are considered in more detail.

2.3.1. Irrigation

Irrigation is one of the important agricultural management practices that have a major effect on soil properties, and consequently, affect soil moisture and nutrient transport for plant growth and developmental characteristics (Ascough II et al., 2008). In plants, water availability meaningfully affects all physiological processes which contribute to plant morpho-physiological response, primary, and secondary metabolism (Kleinwächter and Selmar, 2015). Xue et al. (2018) examined the effects of different irrigation regimes on plant growth indicators and chemical composition of *Cassia obtusifolia* L. seed, which is known to possess antihypercholesterolemic and antihyperglycemic properties. The authors observed that a reduction in protein content (from 39.48 to 34.84mg/g) and plant growth factors except seed yield, but an increase in anthraquinone content (from 2.873 to 6.321 mg/g) at lower water availability (70% field capacity). They concluded that increased anthraquinones content may connect to the seed yield that was unaffected by water stress. Furthermore, a study done by Huot et al. (2014) showed that there is growth–defense trade-offs under stressful environmental factors that led to producing predominantly secondary metabolites in response to water deficit that could explain enhanced anthraquinone content at a mild irrigation treatment in *Cassia obtusifolia* L. species. Based on previous work highlighted, water deficit is stated as another important abiotic factor that substantially influences primary and secondary metabolites concentrations by changes in P5CS gene expression linked to carbohydrate metabolism and genes involved in polyphenol production,

thereby affecting subsequent pharmaceutical properties (Elhani et al., 2019). However, Marino et al. (2019) reported that although the concentration of phytochemicals in *Mentha spicata* was not influenced by different irrigation regimes, the yield of essential oils was significantly altered under the application of different regimes of irrigation. Based on their results, the lowest photosynthetic activity, growth traits, and the accumulation of secondary metabolites were observed under strong water stress due to a considerable reduction in total biomass, leaf area, and fresh weight. Herrera et al. (2019), investigated the effects of irrigation treatments including severe drought (SD), restricted irrigation (RI), and full irrigation (FI) on the biosynthesis of several phytochemicals in the common bean (*Phaseolus vulgaris* L.). According to their results, optimal irrigation application (mild hydric stress RI) effectively induced biosynthesis of secondary metabolites including phenolics, flavonoids, glycosides, and terpenoids, as further confirmed by Kusvuran and Dasgan (2017). The authors found that under irrigation deficit, the stomatal closure in the leaves is regulated by abscisic acid signaling mediator, resulting in a drastic reduction in carbon fixation. Irrigation deficit also reduces the amount of energy needed to decrease CO₂ and non-structural carbohydrates; thus, it has significant increase ROS accumulation in the photosynthetic electron transport chain. To detoxify ROS molecules, the synthesis of non-enzymatic antioxidants (i.e., carotenoids, flavonoids, ascorbic acid, and α -tocopherol) and enzymatic antioxidants (i.e., catalase and peroxidase) are encoded by the genes involved in synthesis of phenylalanine ammonia lyase (Pal2), chalcone synthase (Chi), chalcone isomerase (Chs), flavonoid 3'-hydroxylase (F3'h), flavonoid 3'4'-hydroxylase (F3'5'h), and flavonol synthase (Fls) to inhibit cell damage and oxidative damage (Herrera et al., 2019; Gharibi et al., 2019). In agreement with these results is the work of Zhang et al. (2017b), where water stress in *Stellaria dichotoma* L., showed adverse effects on growth characteristics and yield, whereas moderate water stress effectively increased phytochemicals such as flavonoids and saponins. In addition, Vosoughi et al. (2018) observed that the level of essential oils, phenolic, and flavonoid compounds, as well as the antioxidant potential in *Salvia officinalis* L., were influenced by different irrigation frequencies. Their results demonstrated that under decreased irrigation regimes the antioxidant properties and production of total phenolics, flavonoid compounds, and essential oils were promoted by applying a chitosan elicitor that can relate to stimulate metabolic pathways of bioactive compounds. Moreover, Rodrigues et al. (2019) demonstrated that irrigation with different salinities (ranging from 0, as control, to 600 mM) had different effects on growth factors, plant production, and phytochemical content as well as *in vitro* biological antioxidant and anti-inflammatory properties in *Polygonum maritimum* L. The results demonstrated that irrigation with fresh water and mild salinity significantly had the highest effects on growth, productivity, total phenolic compounds (300 mM salinity: 107 mg GAE/g DW) total flavonoids (200 mM salinity: 26.1 mg GAE/g DW), and *in vitro* anti-inflammatory action (fresh water: 79.7% nitric oxide reduction at 100 μ g/mL) and *in vitro* antioxidant capacity (fresh water:

96.2% radical-scavenging activity of DPPH at 1 mg/mL) by affecting the activity of oxidases/dehydrogenases, redox status and relevant genes expression linked to synthesis of biochemical compounds under different irrigation treatments.

As irrigation has a significant effect on the biosynthesis of phytochemicals and pharmaceutical activities, more studies should be carried out to gain the optimal degree of irrigation correlated with the increasing yield of bioactive compounds and their subsequent biological potential.

2.3.2. Fertilizers

Implementing appropriate chemical fertilizers and/or organic manures at the right time can supply plants with the required nutrients necessary for optimal growth and production of phytochemicals (Khalid et al., 2017). Ibrahim et al. (2013) clarified that organic fertilizers significantly influence the improvement of soil physicochemical properties and health, which sequentially affect growth responses and nutritional value. In the related study carried out by Yin et al. (2018), nitrogen (N), phosphorus (P), and potassium (K) fertilizers application effectively promoted plant growth indices and yield in *Vigna radiata* L. However, applying different ratios of N, P and K indicated different effects on the plant production and growth parameters of *Vigna radiata* L. From this study, it can be postulated that NPK fertilizer ameliorated growth traits by (1) inducing the biosynthesis of primary metabolites (e.g., proline, sugar, and chlorophyll), (2) increasing pathogen resistance by inducing the phytonutrient biosynthetic pathways (Mondal et al., 2017). Ibrahim et al. (2013) stated that applying organic fertilizer like chicken manure significantly increased the yield of phytochemicals such as total phenolic compounds (1.32 mg/g gallic acid dry weight), flavonoids (0.81 mg/g rutin dry weight), glutathione (632.16 nmol/g dry weight), and saponin (38.16 mg/g) concentrations and antioxidant potential in *Labisia pumila* Benth, in comparison with inorganic fertilizer like NPK. They also found a higher level of soluble sugar in plants treated with the organic fertilizer that may explain enhanced secondary metabolites production. In previous studies conducted by Jaafar et al. (2012), there was a positive correlation between carbohydrate content and biosynthesis of flavonoid and phenolic compounds of *Labisia pumila* Benth. Additionally, higher micronutrient levels were found in plants treated with organic fertilizers that properly supplied required elements for cellular chemical reactions, resulting in increased phytochemical production and relevant biological activities (Ibrahim et al., 2013). Several studies demonstrated that gallic acid and rutin have potent antidiabetic properties due to their higher potency in scavenging ROS and superior hydroxylation degree (Saravanan and Parimelazhagan, 2014). Therefore, applying organic fertilizers to improve targeted phytochemicals used in treating diabetes is a practical strategy in indoor sustainable agricultural systems. In the related study done by Khalid et al. (2017), the use of organic fertilizer and biofertilizer such as fungus had favorable effects on growth characteristics, yield, nutritional values, and phytochemical compositions including phenolics, flavonoids, and phenolic

acid in *Brassica campestris* ssp. *chinensis* L. Their findings showed that mixture of organic fertilizer and biochar (OB) was the most effective growing media in boosting total flavonoids and phenolic acid. This mixture may relate to the stimulatory effects of OB on early (CHS, CHI, and F3H) and late (FLS and ANS) gene expressions. Encoding enzymes involved in the conversion of 4-coumaroyl-CoA precursor to other intermediate compounds used in the biosynthesis pathway of flavonoids. Also, the results indicated the higher antiradical and anti-inflammatory properties of profiled phytochemicals in the inoculated plants by OB which were associated with the inhibition of enzymes involved in the inflammatory process (Khalid et al., 2017). Al-Kharusi et al. (2009) revealed that organic fertilizers were more effective in enhancing secondary metabolites production in date fruit (*Phoenix dactylifera*) and antioxidant activities in cabbage (*Brassica oleracea*) compared with their mineral fertilizer counterparts.

Since limited research has been reported on how chemical fertilizers and/or organic manures influence plant bioactive compounds and their medicinal activities, more studies should be conducted on this subject matter. Such data will provide detailed information on the relationship between various fertilizers, the yield of plant phytochemicals, and their final bioactive properties (i.e., antioxidant and antidiabetic properties).

3. Plant Phytochemicals and Their Role in Diabetes

According to Arumugam et al. (2013), a variety of herbal plants that are successfully able to prevent/control diabetes and its complications have been reported in the literature. Based on the literature, there are approximately 800 plants with antidiabetic properties, some of which have been assessed by several experimental techniques (Arumugam et al., 2016; Arunachalam and Parimelazhagan, 2012). Table 1 demonstrates examples of 44 medicinal plants with potent antidiabetic properties. Several important traits connected to these plants including the family of plant species, the type of extracts gained from different parts of the plant (i. e., root, leaves, and shoot), their secondary metabolites, biological activities, as well as brief anti-diabetic or anti-hyperglycemic activities of these plants' extracts are detailed in the table.

4. Secondary Metabolites

Secondary metabolites are non-nutritive organic compounds biosynthesized by plants, bacteria, and fungi. Though they are not directly associated with primary metabolic activities such as growth, development, or reproduction of an organism, they are vital for the plants to survive and persist in their environment (Bartwal et al., 2013). Based on the origin of their biosynthesis, plant phytochemicals are classified into three main categories: namely phenolics, terpenoids, and sulfur- and nitrogen-containing alkaloids compounds (Crozier et al., 2008). They can provide long-term advantages to the plants such as protection against environmental stress (Rosenthal and

Table 1. Antidiabetic properties of some selected medicinal plants.

No.	Plant name	Family	Type of extract	Secondary metabolites	Bioactive activity	Outcome (effects)	References
1	Sage-leaved alangium (<i>Alangium lamarkii</i> Thwaites)	Alangiaceae	Alcoholic leaves extract	Alkaloids, Terpenoids, Steroids, Tannins, Phenols	Antidiabetic and antihyperglycemic	Balancing blood glucose levels, restoring liver glycogen, and enhancing the activity of antioxidant enzymes	Kumar et al. (2011c)
2	Black Siris (<i>Albizia odoratissima</i> Benth)	Mimosaceae	Methanolic bark extract	Steroids, Tannins, Phenolics, Saponins	Hypoglycemic	Reducing the level of sugar, total cholesterol, and triglycerides in the bloodstream	Kumar et al. (2011a)
3	Cashew (<i>Anacardium occidentale</i> L.)	Anacardiaceae	Ethanol leaves extract	Glucosides, Flavonoids, Phenolic compounds	Antidiabetic	Reduction in the blood sugar levels, serum insulin, glycated hemoglobin levels, serum lipid parameters	Abdullahi and Olatunji (2010)
4	Kale (<i>Brassica oleracea</i> var. <i>acephala</i>)	Brassicaceae	Methanolic extract	Glucosinolates, Anthocyanins, Phenylpropanoids, Carotenoids	Antihyperglycemic	Reduction in hyperglycemia & CHC ₁ fraction acts as an insulin sensitizer	Yoshida et al. (2007)
5	Java Tea, Cat's Whiskers (<i>Orthosiphon aristatus</i> Boldingh)	Lamiaceae	Methanol shoot extract	Phenolic compounds, Phenylpropanoids, Glucosinolates	Antidiabetic	Preventing the generation of lipid peroxidation products resulting in decreasing oxidative stress	Hunaefti et al. (2018)
6	Chinese mustard (<i>Brassica juncea</i> L.)	Cruciferae	Aqueous seed extract	Glycosides, Flavonoids, Phenolic compounds, Sterols, Triterpene, Glucosinolates	Hypoglycemic	Improved state of availability of insulin to regulate the level of the blood sugar	Thirumalai et al. (2011); Parikh and Khanna (2014)
7	European Barberry, Common barberry (<i>Berberis vulgaris</i> L.)	Berberidaceae	Aqueous root extract	Tannins, Alkaloids, Saponins, Sterols, Anthraquinones	Hypoglycaemic	Regulation glucose, cholesterol, and triglycerides levels in the bloodstream as well as an increase in insulin release and restoration of metabolic activities.	Meliani et al. (2011)
8	Goldthread (<i>Coptis trifolia</i>)	Ranunculaceae	Not published	Alkaloids compounds	Hypoglycemic	Not published	Elias and Dykeman (1982)
9	Teri pods (<i>Caesalpinia digyna</i> Rottler.)	Fabaceae	Methanol root extract	Flavonoids, Tannins, Steroids, Triterpenoids, Glycosides	Antidiabetic	Regulate blood glucose concentration by controlling amylase and glucosidase enzymes actions	Narkhede et al. (2011)
10	Ivy Gourd (<i>Coccoloba grandis</i> L.)	Cucurbitaceae	Aqueous leaves extract	Flavonoids, Phenolic compounds, Alkaloids, Glycosides	Anti-hyperglycemic and Antihyperlipidemic	β-cell regenerative by regulation of intracellular glucose homeostasis and reduction in the concentration of serum cholesterol and triglycerides	Atanayake et al. (2016); Kondhare and Lade (2017)
11	Bweribodele, Epakum (<i>Curculigo Ploosa</i>)	Hypoxidaceae	Corn steep liquor extract	Phenolic compounds like Saponin, Terpenoid, coumarin, Steroid.	Antidiabetic	Decrease in blood glucose concentration	Karigidi and Olaitiya (2020)
12	Silk-cotton or Kapok tree (<i>Ceiba pentandra</i>)	Malvaceae	Methanol extract of stem bark	Terpenoids, Flavonoids, Tannins, Saponins, Glycosides.	Antidiabetic	Reduction in blood glucose level and restoring reduced hematological parameters	Odoh et al. (2016)
13	Tanner's Cassia, Mature Tea Tree (<i>Cassia auriculata</i> L.)	Caesalpinaceae	Aqueous leaves extract	Flavonoids, Alkaloids, Phenolics, Saponins, Tannins, Glycosides.	Antihyperglycemic	Increased levels of free radical-scavenging and/or decreased level of lipid peroxidation. Reduce blood glucose level	Gupta et al. (2011)
14	East Indian Sainwood, Yellowwood (<i>Chloroxylon swietenia</i> DC)	Rutaceae	Aqueous and methanolic root extracts	Alkaloids, Coumarins, Flavonoids, Steroids	Antidiabetic	Regulating plasma insulin levels. Adjusting plasma insulin concentration. Regeneration and regulate the carbohydrate metabolic enzymes and glycogen actions in the liver tissue.	Jayaprasad et al. (2016)
15	Sweet Datoak (Datarium microcarpum)	Fabaceae	Methanol root extract	Terpenoids, Saponins, Resins, Glycosides, Flavonoids	Hypoglycemic and Antidiabetic	Increased insulin secretion	Okolo et al. (2012)
16	Elephant Apple (<i>Dillenia Indica</i> L.)	Dilleniaceae	Methanolic leaves extract	Phenolic compounds, Tannins, Carotenoids, Saponins, Terpenoids	Antidiabetic and Hypolipidemic	Reduction in the concentration of blood glucose, cholesterol, and triglycerides or/and prevention of endogenous glucose production and regulation of the bodyweight	Kumar et al. (2011b)
17	Chota-kirayata (<i>Eicosentema litorea</i> Blume)	Centianaceae	Aqueous extract of the whole plant	Alkaloids, Triterpenoids, Sterols, Saponins, Steroids, essential oil	Antidiabetic	Reduction in blood glucose level, urea, creatinine, lipid, cholesterol, and triglycerides	Sonawane et al. (2010)
18	Shan-Zhi-Ma (<i>Helicteres angustifolia</i> L.)	Sterculiaceae	Ethanol root extract	Phenolic compounds, Flavonoids, Triterpenoids, Quinines, Lignans	Antidiabetic	Increased in glucose uptake and reduction in the insulin resistance	Hu et al. (2016)

Table1. Continued...

No.	Plant name	Family	Type of extract	Secondary metabolites	Bioactive activity	Outcome (effects)	References
19	Wilayati tulsi (<i>Hyptis suaveolens</i> : L)	Lamiaceae	Methanolic extract	Alkaloids, Tannins, Saponins, Flavonoid, Terpenoids	Antidiabetic	Modulate blood glucose concentration through reduction of serum triglycerides and total cholesterol and other biochemical parameters.	Poonkodi et al. (2017)
20	Spade flower (<i>Hybanthus emmeaspermus</i> L.)	Violaceae	Alcoholic extract of the whole plant	Phenolic compounds, Flavonoids, Alkaloids, Terpenes, Glycosides, Saponins, Tannins	Hypoglycemic and Antidiabetic	Decrease glucose level	Patel et al. (2011)
21	Lippia (<i>Lippia nodiflora</i> L.)	Verbenaceae	Methanol extract of the whole plant	Saponins, Sterols, Tannins, Flavonoids, Coumarins, Quinones	Antidiabetic and Hypolipidemic	Decrease blood sugar level and restoration of pancreatic β -cells	Balamunagan and Ignacimuthu (2011)
22	Sweet tea (<i>Lithocarpus polystachyus</i> Rehd)	Fagaceae	Ethanol & Aqueous leaves extract	Flavonoids, Polyphenols, Sterols	Hypoglycemic	Decrease glucose level, total cholesterol, triglyceride, lipid as well as urea, nitrogen, creatinine in the blood. Improve antioxidant potential.	Wang et al. (2016); Hou et al. (2011)
23	Giant yellow mulberry (<i>Myrianthus arboreus</i> F.)	Moraceae	Ethanol stem bark extract	Flavonoids, Alkaloids, Phenolics, Triterpenoids, Tannins, Sterols, Saponins, Glycoside compounds	Hypoglycaemic and Antihyperlipidemic	Decreased urea and blood creatinine concentration. Adjusted glucose, cholesterol, triglycerides, lipids levels in blood serum	Dickson et al. (2016)
24	White Horsehound (<i>Marrubium vulgare</i> L.)	Lamiaceae	Methanolic extract	Flavonoids, Tannins, Terpenoids, Alkaloids, Phenylpropanoids Esters, Phenolic compounds	Antidiabetic	Increasing insulin secretion from pancreatic β -cells and preventing the process of insulin degradation	Boujdjal et al. (2012); Elberry et al. (2015); Bouterfas et al. (2014)
25	Savulikodi (<i>Merremia tridentata</i> L.)	Convolvulaceae	Aqueous root extract	Diosmetin, Luteolin, Glucosides	Antidiabetic	Decrease of glucose and lipid profile of STZ in blood serum	Arumachalam and Parimelazhagan (2012)
26	Tulsi, holy basil (<i>Ocimum sanctum</i> L.)	Lamiaceae	Methanolic extract	Triterpenoids, Flavonoids, Phenolic compounds	Antidiabetic and Hypoglycemic	Decrease the blood glucose cholesterol, triglycerides levels. & The presence of Zing element in plant	Patil et al. (2011); Pattanayak et al. (2010)
27	Mexican mint (<i>Plectranthus amboinicus</i> minis)	Lamiaceae	Ethanol extract	Flavonoids, Phenolics, Terpenoids	Antidiabetic and Hypoglycemic	Reduced level of blood sugar by regulation of carbohydrate metabolizing enzyme	Koti et al. (2011); Zhang et al. (2017a)
28	Purslane (<i>Portulaca oleracea</i> L.)	Portulacaceae	Aqueous leaves extracts	Flavonoids like quercetin, kaempferol, luteolin, apigenin.	Hypoglycemic and Hypolipidemic activities	Reduced blood glucose, triglycerides, LDL-cholesterol concentration but enhanced HDL-cholesterol level	Moukette et al. (2017)
29	Honey mesquite (<i>Prosopis glandulosa</i> Torr.)	Fabaceae	Gelatin/jelly of the whole plant	Flavonoids, Steroids, Alkaloids, Terpenoids	Antidiabetic	Stimulation of insulin release and improvement of insulin sensitivity	George et al. (2011); Kumar et al. (2011d)
30	Foxtail millet (<i>Setaria italica</i>)	Poaceae	Aqueous seed extract	Steroids, Alkaloids, Carbohydrates, Glycosides	Antihyperglycemic	Control blood glucose, triglycerides, total cholesterol such as LDL and VLDL cholesterol (bad cholesterol)	Sireesha et al. (2011)
31	Toothache plant (<i>Spilanthes Africana</i> Murr)	Asteraceae	Aqueous leaves extracts	Phenolic compounds, Flavonoids, Tannins, Polyphenols Alkaloids, Terpenoids, Coumarins, acetylenes, lactones	Hypoglycemic and Hypolipidemic	Reduced blood glucose, triglycerides, LDL-cholesterol concentration, and improved HDL-cholesterol (good cholesterol)	Moukette et al. (2017)
32	Asoka Tree (<i>Saraca asoca</i> Roxb)	Caesalpinaceae	Methanol extract	Tannin, Flavonoid, Saponin, Glycosides, Steroids	Antihyperglycemic	Controlling glucose concentration in blood	Kumar et al. (2012); Saha et al. (2012)
33	Turkey berry (<i>Solanum torvum</i> Swartz)	Solanaceae	Methanol Fruit extract	Methyl caffeate (a phenol constituent), Flavonoid sulfate, Steroidal glycosides	Antihyperglycemic	Decreased glucose level and regeneration pancreatic β -cells	Gandhi et al. (2011)
34	Parala, Pachotti, (<i>Symplocos cochinchinensis</i> L.)	Symplocaceae	Hexane leaves extract	Steroids, Triterpenoids, Phenolic compounds	Antidiabetic	Improved insulin sensitivity and reduced the level of cholesterol, triglycerides, and lipids (free fatty acids) in blood plasma	Sunil et al. (2011)
35	Arrow-leaf sida (<i>Sida rhombifolia</i>)	Malvaceae	Aqueous leaves extracts	Flavonoids, Tannins, Polyphenols, Mucilages, Triterpenoids	Hypoglycemic and Hypolipidemic	Decreased in blood sugar, triglycerides, LDL-cholesterol level and promoted the HDL-cholesterol level.	Moukette et al. (2017)

Table1. Continued...

No.	Plant name	Family	Type of extract	Secondary metabolites	Bioactive activity	Outcome (effects)	References
36	Yellow-berried Nighthshade (<i>Solanum xanthocarpum</i>)	Solanaceae	Methanolic leaves extract	Flavonoids, Alkaloids, Saponin, Sterols, Glycosides	Antihyperglycemic	Decreased lipid peroxidation and improved antioxidant enzymes potential	Poongothai et al. (2011)
37	Stinging Nettle (<i>Urtica dioica</i> L.)	Urticaceae	Hydroalcoholic leaves extract	Flavonoids, Tannins, Scopoletin, Sterols, fatty acids	Hypoglycemic	Regulating glucose concentration and insulin resistance in blood	Ahangarpour et al. (2012); Asgarpanah and Mohajerani (2012)
38	Saudi mistletoe (<i>Viscum schimperi</i> Engl)	Viscaceae	Methanolic aerial parts extract	Polysaccharides, Oligosaccharides, Alkaloids	Antihyperglycemic and Hypolipidemic	Decreased the level of sugar, triglycerides, LDL-cholesterol in blood as well as stimulation and potentiation of insulin release	Abdel-Sattar et al. (2011)
39	Chinese chaste tree (<i>Vitex negundo</i> L.)	Lamiaceae	Methanolic leaves extract	Volatile oils, Flavonoids, Iridoid glucoside	Antihyperglycemic	Improved insulin release from β -cells in pancreatic tissue by iridoid glucoside as well as increased glucose uptake and metabolism and reduced blood glucose level	Sundaram et al. (2012)
40	Tetraena alba (<i>Zygophyllum album</i>)	Zygophyllaceae	Ethanol extract of Whole plant	Phenolic compounds, Flavonoids, Carbohydrates, tannins	Antidiabetic	Decreased blood glucose concentration, lipid peroxidation. Reinforced defence systems by increasing potential enzymatic and nonenzymatic antioxidants	Ghoul et al. (2011)

Berenbaum, 2012). In addition, secondary metabolites give plants their characteristic features such as color and smell that attract potential pollinators. The amounts of secondary metabolites in plants were increased when exposed to herbivores or pathogens (Rosenthal and Berenbaum, 2012).

Apart from the importance of these compounds for adaptation to environmental stressors, they also exhibit practical applications in the medicinal, nutritional, and cosmetic companies (Jensen et al., 2014). Secondary metabolites have been proven to exert an extensive range of bioactive actions including antidiabetic, antioxidant, antimicrobial, anti-inflammatory, antiviral, anticancer, and antifungal activities (Kholkhal et al., 2013; Atanasova-Penichon et al., 2016). Antioxidant activities of plant-based chemical compounds illustrate potent inhibitory effects against inflammation responsible for insulin resistance and oxidative stress correlated with diabetes and cardiovascular diseases (Bajaj and Khan, 2012; Jung et al., 2014). As antioxidants, secondary metabolites have various therapeutic strategies including inhibiting free radical formation, eliminating free radicals, and enhancing the capabilities of endogenous antioxidant enzymes (Hamilton et al., 2007).

4.1. Phenolic compounds

Phenolic compounds are one of the major groups of bioactive compounds. Several physical characteristics of plants are connected to these compounds. They are directly involved in plants' taste, smell, and color. Not only are these compounds play a vital role in the growth, development, and defense mechanism in plants, ample research has shown their remarkable impacts on human health (Sun et al., 2008). Phenolic compounds possess various anti-aging, anti-inflammatory, and antioxidant functions, which can decrease the risk of acute diseases like diabetes, various types of cancer, and cardiovascular disease (Lin et al., 2016). The high antioxidant capacities of phenolic compounds have an important role in managing and controlling diabetes progression and its relevant complications via modulating starch and lipid digestion, reducing hyperglycemia and insulin resistance, improving β -cells' ability to produce insulin, and preventing oxidative stress (Asgar, 2013; Lin et al., 2016).

4.1.1. Anthocyanins

Anthocyanins are phenolic compounds sub-grouped under flavonoids. Anthocyanins are known as water-soluble pigments that depend on environmental pH, they appear red, purple, or blue (Ghosh and Konishi, 2007). Anthocyanins have an antioxidant function in plants against reactive oxygen species caused by biotic and abiotic stresses (Qiu et al., 2016). Furthermore, they are known to serve as attractants for pollination and seed dispersal (Saito and Harborne, 1992). In human health, they have been proven to have a significant role in vision health by eliminating retinal inflammation (Miyake et al., 2012). In addition, anti-mutagenic, anti-carcinogenic, and anti-microbial properties have been attributed to anthocyanin-rich foods/plants. The antidiabetic activities of anthocyanins are primarily correlated to their antioxidant capacities

(Sancho and Pastore, 2012). The antioxidant properties of anthocyanin are closely connected to the number of hydroxyl groups present in their ring B (Guo and Xia, 2018; Sancho and Pastore, 2012). Anthocyanins control diabetes in two different ways; namely, prevention of oxidative stress and stimulation of β -cells to secrete insulin (Li et al., 2013). Thus, anthocyanin-rich foods/plants have a high potential to protect against diabetes and cardiovascular diseases.

4.2. Carotenoids

Carotenoids are plant pigments categorized under tetraterpenoids. They have a vital role in fruit and vegetable colors (Sluijs et al., 2015). Various physiological properties including antidiabetic, antioxidant, anti-inflammation, and anti-obesity activities have been ascribed to carotenoids (Roohbakhsh et al., 2017; Sanjeevi et al., 2019). Carotenoids' high antioxidant capacity considerably affects the management and reduction of T1DM, T2DM, and associated complications like obesity and heart and blood vessel disease (Sanjeevi et al., 2019). Roohbakhsh et al. (2017) stated that oxidative stress and inflammation are two main components associated with the development of T2DM due to impaired insulin secretion and enhanced insulin resistance. Carotenoids can restrain oxidative stress and inflammation as well as regulate immune system activity by reducing chemokine and cytokine secretion which are the main factors in insulin resistance. Additionally, carotenoids adjust lipid metabolism in adipose tissues, thus, acting as an anti-obesity factor (Voutilainen et al., 2006; Maeda et al., 2008).

4.3. Glucosinolates

Glucosinolates are another plant phytochemicals mainly discovered in the Brassicaceae family (Ma et al., 2018). They are present as salts of sulfate synthesized from various amino acids. There are more than 120 diverse glucosinolates based on the type of amino acid from which they are synthesized (Soledade et al., 2010). Recent studies showed glucosinolates as antimicrobial, anti-inflammation, and antioxidant compounds (Bischoff, 2016). Like other secondary metabolites mentioned in this review, glucosinolates can reduce the risks of T2DM by their capacity to limit oxidative stress and inflammation (Jeon et al., 2018).

Overall, there are many health benefits of plant secondary metabolites on human health. Having properties like antioxidative, α -amylase, and α -glucosidase properties makes these molecules a great potential in reducing chronic diseases related to obesity and diabetes.

5. Diabetes

Diabetes is a metabolic disorder related to impaired insulin secretion or insulin insensitivity of the body cells to insulin (Chiang et al., 2014). Diabetes is divided into three classes including Type I Diabetes Mellitus (T1DM), Type II Diabetes Mellitus (T2DM), and gestational diabetes mellitus (Choudhury et al., 2018). The pancreas of a person with T1DM does not produce adequate insulin, with infected

persons completely dependent on the use of external insulin (Arumugam et al., 2013). In contrast, a person with T2DM has insulin resistance leading to a decline in insulin sensitivity. Another category of diabetes called gestational diabetes mellitus can be found in pregnant women with no previous diagnosis of diabetes (Choudhury et al., 2018). Diabetes is known as one of the major widespread diseases and is the fourth leading cause of death (Bahmani et al., 2014). According to the World Health Organization report, that approximately 425 million people were diagnosed with diabetes globally in 2017, which may enhance to 629 million by 2045. The Canadian Community Health Survey (CCHS) reported that around 2.27 million Canadians were diagnosed with diabetes in 2017.

In comparison with T1DM, the causes and complications of T2DM can be effectively managed or controlled through healthy lifestyles and dietary choices. Some important factors associated with the steady rise in diabetes include obesity, physical inactivity, and aging (Choudhury et al., 2018). Research has shown a strong connection between T2DM and obesity. Obesity is one of the main causes of T2DM because excess fat makes a significant contribution to insulin resistance, causing an increase in blood glucose concentration (Saad et al., 2017). Having a healthy diet such as adjusting carbohydrates intake is one of the most effective ways of losing weight and balancing blood sugars. Consuming nutritious high-fiber foods and vegetables can provide the essential vitamins and minerals needed to help decrease risks of obesity and T2DM (Arumugam et al., 2013; Saad et al., 2017). Additionally, the use of medicinal plants is another effective approach to avoid or manage T2DM (Hahn et al., 2020).

5.1. Evaluation of anti-diabetic potential

Regulation of α -amylase and α -glucosidase enzymes actions is an effective and practical way to control hyperglycemia (Sekhon-Loodu and Rupasinghe, 2019). Although synthetic drugs including acarbose and miglitol are used to restrain α -amylase and α -glucosidase potential, research has associated their use with negative side effects such as dizziness, headache, flatulence, and diarrhea. Thus, medicinal plants which possess potential antidiabetic benefits are safer alternatives (Patel et al., 2011). Previous researchers have confirmed that the composition of the secondary metabolites of medicinal plants has potent inhibitory actions against α -amylase and α -glucosidase (Patel et al., 2012).

6. Conclusion

Considering the high global demand for natural foods and functional plants for the prevention or management of diabetes, there is a need for sustainable production systems. However, variations in preharvest factors can significantly influence plant growth, development, and biosynthesis of phytochemicals with positive health benefits. Nevertheless, the effects of preharvest factors on the antidiabetic properties of food crops and medicinal plants are not explicit nor easily accessible in the literature. Findings of this review showed that the biosynthesis of

secondary metabolites responsible for the antidiabetic potential of food crops and medicinal plants are largely influenced by preharvest factors. For future perspectives, optimum preharvest parameters should be investigated to provide in-depth data for developing new functional foods with top-notch antidiabetic properties.

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