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Review

Phytochemistry and mode of action of some tropical spices in the management of type-2 diabetes and hypertension

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Spices are important food supplements and/or food products, which have been used as flavouring agents and preservatives for thousands of years in tropical Africa, Asia and other parts of the world. They are well known for their medicinal properties, and their use in traditional systems of medicine has been on record for a long time. Although, epidemiological and clinical studies have indicated that spices are important source of natural antioxidant having the digestive stimulant action, bioavailability enhancement nature, carminative attribute, antimicrobial activity, hypolipidemic property, antidiabetic influence, antioxidant capacity, anti-inflammatory ability, anticarcinogenic potential and neuroprotective effect. The present review reports the phytochemical constituents and mode of action of some tropical spices as antidiabetic and antihypertensive agents. The conclusion of this review may help in undertaking research for the development of functional foods and nutraceuticals.

Key words: Spices, type-2 diabetes, hypertension, enzymes, antioxidant, phenolics, phytochemicals.

INTRODUCTION

Spices are food supplements or food products, which have been used not only as flavoring and coloring agents, but also as food preservatives and herbs in folk medicines for thousands of years in Africa, Asia and other parts of the world (Srinivasan, 2005a). They are consumed as whole spices or ground into powder and mixed with diets containing cereals, legumes, nuts, fruits, vegetables, milk and milk products. They are also used in soup preparation in various homes and serve as ingredients in the preparation of several traditional delicacies. Spices are utilized as herbs, mainly in the form of isolates from their extracts. Spices are considered to be good contributors to the total nutrient intake of protein, carbohydrates, fats, vitamins and minerals, thereby enhancing the nutritional quality of diets (Pradeep et al., 1993). Apart from the nutrients supplied by spices, they possess many phytochemicals which are potential sources of natural antioxidant such as phenolic diterpenes, volatile oils, flavonoids, terpenoids, carotenoids, phytoestrogens, and phenolic acids (Cai et al., 2004; Suhaj, 2006; Kennedy et al., 2011).

Spice phytochemicals such as curcumin (turmeric), capsaicin (red chillies), eugenol (cloves), linalool (coriander), piperine (black pepper), zingerone (zinger) and cuminaldehyde (cumin) have been reported to inhibit lipid peroxidation (Shobana and Naidu, 2000; Oboh and Rocha, 2007). In recent times, spice antioxidants have raised considerable interest among food scientists, manufactures, and consumers because of their natural antioxidants (Lu et al., 2011). Consumers are increasingly aware of the risk posed by synthetic antioxidants due to their high volatility and instability at elevated temperatures. Therefore, focus has been shifted to the use of natural antioxidants in food preservation (Odukoya et al., 2005; Oboh and Rocha, 2007; Adefegha and Oboh, 2011a).

Food oxidation is considered a major cause of food deterioration and spoilage, causing rancidity in food (Sherwin, 1990). The resultant effect is noticed in the

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decreased nutritional quality, color, flavor, texture and safety of foods. Many spices have also been recognized to possess digestive stimulant action, carminative effect, antimicrobial activity, antioxidant capacity, antiinflammatory property, antimutagenic ability and anticarcinogenic potential (Srinivasan, 2005a). Spices contribute greatly to the daily antioxidant intake in most diets, especially in dietary cultures where spices are used as whole meal (Carlsen et al., 2010). Many spices have been shown to confer health benefits and have been proven to counteract oxidative stress *in vitro and in vivo* (Oboh et al., 2005, 2010a, 2012a; Shan et al., 2005; Wojdylo et al., 2007; Adefegha and Oboh, 2012a). They are common sources of phenolic compounds which have been reported to show superior antioxidant capacity to fruits, cereals, and nuts (Pellegrini et al., 2006; Carlsen et al., 2010). The main active components in spices are phenolic acids, flavonoids and volatile or essential oils (Shan et al., 2005; Wojdyło et al., 2007; Viuda-Martos et al., 2011; Lu et al., 2011).

In Nigeria, over 100 indigenous spices are used as important components of the “African/Nigerian dishes”, bringing original favors and desirable sensory properties to food. Essentially, “Pepper soup” is famous for its sensory, aromatic, attractive, pungency and spicy flavor resulting from the use of bastered melegueta, clove, alligator pepper, ginger, black pepper, garlic, Ethiopian pepper, chili peppers and other spices. Common spices, such as sweet basil, clove, black pepper, turmeric, chili pepper, and ginger are usually part of daily African household meals and also used as traditional African medicine. Numerous studies have reported that spices are important source of natural antioxidant, possessing digestive stimulant action, bioavailability enhancement nature, carminative attribute, antimicrobial activity, hypolipidemic property, antidiabetic influence, anti-inflammatory ability, anticarcinogenic potential and neuroprotective effect (Srinivasan et al., 2004; Shan et al., 2005; Srinivasan, 2005a; Adefegha and Oboh, 2011b).

Diabetes mellitus (DM) is one of the leading causes of global morbidity and mortality, and a major risk for cardiovascular diseases (Alderman et al., 1999). Diabetes mellitus is a metabolic disease characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (World Health Organization (WHO), 1999). The control of postprandial hyperglycemia is an important strategy in the management of diabetes mellitus, especially type 2 diabetis mellitus (T2DM), and reducing chronic complications associated with the disease (Kim et al., 2000; Ali et al., 2006; Ortiz-Andrade et al., 2007). Hence, the inhibition of enzymes (α-Glucosidase and α-amylase) involved in the digestion of carbohydrates can significantly decrease the postprandial increase of blood glucose after a mixed carbohydrate diet, by delaying the process of carbohydrate hydrolysis and absorption and phenolic phytochemicals from spices and have shown promising potentials (Oboh et al., 2010b; Adefegha and Oboh, 2012a).

Hypertension or persistent high blood pressure is a common cardiovascular disease which has become a worldwide problem of epidemic proportions, affecting 15 to 20% of all adults with ailments such as arteriosclerosis, stroke, myocardial infarction and end-stage renal disease (Je et al., 2009). It is regarded as one of the long-term complications of T2DM. These two diseases (hypertension and T2DM) are interrelated metabolic disorders with persistent hypertension being the risk factors for strokes, heart attacks, heart failure and is a leading cause of chronic renal failure (Sowers and Epstein, 1995; Bakris et al., 2000). One of the therapeutic strategies towards the management of hypertension is the inhibition of angiotensin-I converting enzymes (ACE); an enzyme which play a pivotal role in rennin-angiotensin system by converting angiotensin-I to angiotensin-II (potent vasoconstrictor). However, phenolic-rich spices have reported to act as good ACE inhibitors (Ranilla et al., 2010). Therefore, the present review highlights the phytochemical constituents and mechanism of action of some tropical spices as antidiabetic and antihypertensive agents. The pictures of some spices are as shown in Figure 1

Phytochemical composition

Spices in the diet are not considered vital from the nutritional point of view, though they are widely consumed throughout the world. They are not normally included in diet surveys, nor are they suggested or recommended in what are known as balanced diets, probably because it was thought that the intake of these spices was so small that their contribution of nutrients may not be significant (Pradeep et al., 1993). As part of normal diet, plant foods are thus not only a source of nutrients and energy provider, but may confer additional role of providing health benefits beyond their basic nutritional functions (Shahidi and Naczk, 2004). Attention is being focused on identifying dietary phytochemicals which are plant secondary metabolites (array of bioactive constituents) that are capable of eliciting health enhancing effects and disease preventing abilities (Visioli and Galli, 1998).

Phytochemicals describe the chemicals present in different parts of plant organs (leaves, stems, roots, flowers, fruits and seeds). Consumption of food rich in several phytochemicals such as saponins, alkaloids, terpenes, phenylpropanoids, isoprenoids, steroids, coumarins, flavonoids, phenolic acids, lignans, contain chemicals such as flavonoids, terpenoids, lignans, sulfides, polyphenolics, carotenoids, coumarins, saponins and plant sterols with biological activities that may provide therapeutic effects (Dorman et al., 2003, 2004; Cuvelier et al., 2004; Shan et al., 2005; Ninfali et al., 2005; Adefegha and Oboh, 2012b). The presence of

Figure 1. Pictures of spices.

phytochemicals has been shown to contribute immensely to the protective potential against degenerative diseases, therapeutic effects essential to preventing diseases, and nutritional quality of food and food products (Chu et al., 2002; Oboh et al., 2010b).

Our recent study revealed the presence of flavonoid and cardiac glycoside in Ethiopian pepper [*Xylopia aethiopica* [Dun.] A. Rich (Annonaceae)], nutmeg [*Monodora myristica* (Gaertn.) Dunal (Annonaceae)], clove [*Syzygium aromaticum* [L.] Merr. et Perry (Myrtaceae)], ashanti pepper [*Piper guineense* Schumach. et Thonn (Piperaceae)], bastered melegueta [*Aframomum danielli* K. Schum (Zingiberaceae)] and alligator pepper [*Aframomum melegueta* (Rosc.) K. Schum (Zingiberaceae)], tannin in Ethiopian pepper and clove, phlobatanin and anthraquinone in clove and saponin in Ethiopian pepper, clove, ashanti pepper, bastered melegueta and alligator pepper (Adefegha and Oboh, 2012a). Other active components of spices (Figure 2) such as curcumin (turmeric), capsaicin (bird's pepper), eugenol (cloves), linalool (coriander and sweet basil), piperine (black pepper), gingerol (ginger) and allicin (garlic) have been reported to inhibit lipid peroxidation in various tissues (Lawson, 1998; Ursell, 2000; Srinivasan, 2005a; Hiyasat et al., 2009; Adefegha and Oboh, 2011b).

Polyphenols

Food contains several chemicals, many of which have specific biological activity. The chemicals also interact with each other, confounding any effort to identify bioactives. Among these bioactive components are the phenolics. Dietary phenolics are secondary metabolites which are widely present in diets rich in vegetables, fruits, legumes, cereals, nuts, and have been linked to various beneficial effects on human health, such as minimizing the risk of developing coronary heart disease, cancer, hypertension, diabetes, and inflammatory processes (Scalbert et al., 2005; Zafra-Stone et al., 2007). They are present in plants as derivatives and/or isomers of flavones, isoflavones, flavonols, catechins, and phenolic acids.

Phenolic compounds in plants can be divided into two major categories: phenolic acids and flavonoids. Phenolic acids account for about 33% of the total phenolic intake; mainly the derivatives of benzoic or cinnamic acid. Flavonoids, on the other hand account for the remaining 67% of the total phenolic intake (Scalbert and Williamson, 2000). They are regarded as the most abundant polyphenols in human diets, and are mainly divided into: anthocyanins (colourful compounds) and anthoxanthins (colorless compounds), which can be subdivided into flavones, flavans, flavonols, flavanols, isoflavones, and their glycosides (Bravo, 1998; Liu, 2004). Phenolic compounds in plants are usually found either as free or bound forms (Chu et al., 2002; Sun et al., 2002). Free soluble phenolics may be available as aglycones while the bound phenolics may be present as conjugates (glycosides and esters) or attached to the plant cell wall (Rice-Evan et al., 1996).

Hydrolysis by chemical and enzymatic means may be necessary to release the bonds (Stalikas, 2007). Most of the biological actions such as antimicrobial, hypolipidemic, antidiabetic, antilithogenic, antioxidant, antiinflammatory, antimutagenic, anticarcinogenic and neuroprotective properties observed in some spices have been attributed to the presence of phenolic compounds (Cai et al., 2004; Liu et al., 2008; Shan et al., 2005; Wojdylo et al., 2007; Muchuweti et al., 2007; Konczak et al., 2010). Shan et al. (2005) reported that spices from Labiatae, Myrtaceae and Compositae families are rich in rosmarinic acid, caffeic acid and volatile oil. In the same vein, chlorogenic acid, rutin, quercetin, and naringin were also identified as the dominant phenolic compounds in spices from the family Rutaceae (Lu et al., 2011).

In an experiment carried out on phenolic composition of three commercial herbal drugs and spices from lamiaceous species: *Thymi herba* (thyme), *Serpylli herba* (wild thyme) and *Majoranae herba* (sweet marjoram) using high performance liquid chromatography (HPLC) and high performance thin layer chromatography (HPTLC) methods, luteolin-7-O-β-glucuronide, lithospermic acid, rosmarinic acid and methyl rosmarinate, together with other known compounds, were detected and quantified. Luteolin-7-O-β-glucuronide and lithospermic acid were identified as novel wild thyme constituents, luteolin-7-O-β-glucuronide and methyl rosmarinate as novel compounds in sweet marjoram.

Methyl rosmarinate was found to be present in thyme. The amount of polyphenol investigated in herbal drugs and spices has reached 84.3 mg/g dried spices (Fecka and Turek, 2008). Previous report on phenolic composition of thyme indicated the presence of caffeic acid, rosmarinic acid, apigenin, luteolin, luteolin-7-O-β-glucuronide, luteolin-7-O-β-glucoside, 6-hydroxyluteolin glycosides, polymethoxyflavones, narirutin, eriodictyol, eriocitrin, hesperidin and taxifolin (Dapkevicius et al., 2002; Haraguchi et al., 1996; Kobayashi et al., 2003; Kosar et al., 2005; Miura et al., 2002; Watanabe et al., 2005). Wojdyło et al. (2007) also identified and quantified major phenolics by reverse-phase high-performance liquid chromatography (RP-HPLC) in thirty two (32) selected herbs and spices. The prominent phenolic acids reported were caffeic, p-coumaric, ferulic and neochlorogenic acids while the flavonoids detected were quercetin, luteolin, apigenin, kaempferol and isorhamnetin. Caffeic acid was reported as the predominant phenolic compound in sage (*Salvia officinalis*) (296 mg/100 g dry weight), thyme (*T. vulgaris*) (517 mg/100 g dry weight) and oregano (*Origanum vulgare*) (649 mg/100 g dry weight).

Luteolin (616 mg/100 g dry weight) and caffeic acid (406 mg/100 g dry weight) were also present in

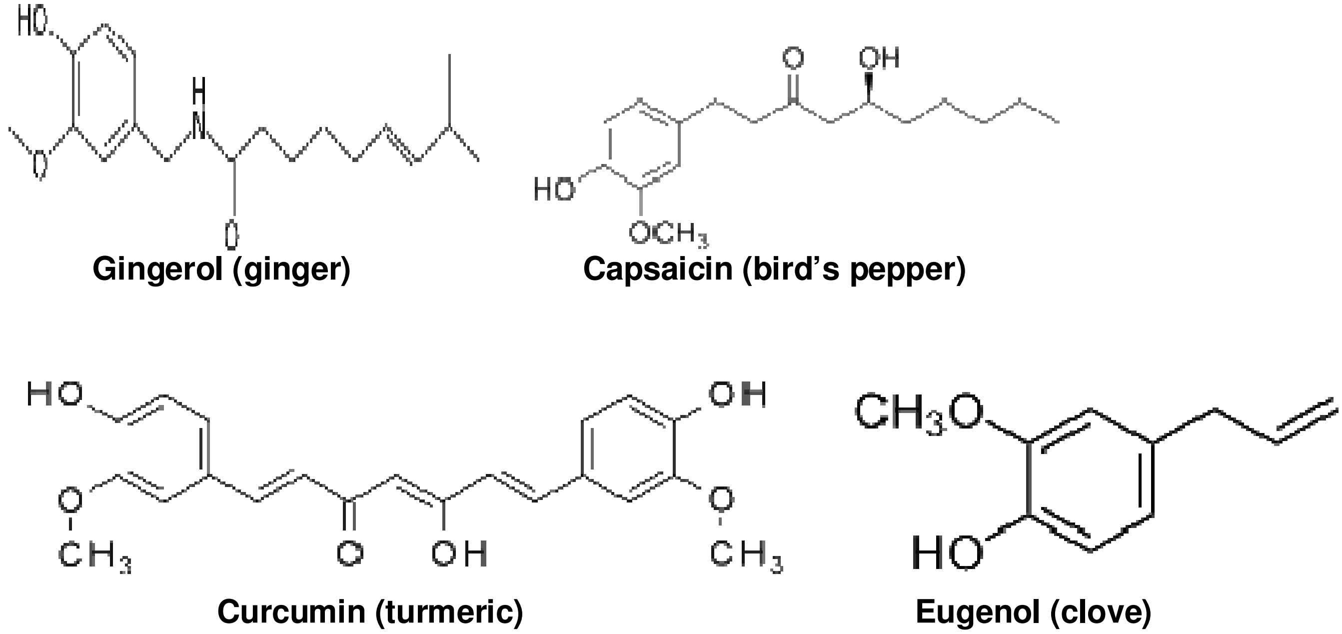

Figure 2. Active ingredients of biological relevance present in abundance in some spices.

abundance in rosemary (*Rosmarinus officinalis*). Turmeric (*Curcuma longa*) was reported to contain p-coumaric acid (5.96 mg/100 g dry weight) and ferulic acid (17.6 mg/100 g dry weight) in small quantities. A minute amount of ferulic acid was reported to be present in nutmeg (*M. fragrans*). Quercetin was the only phenolic compound detected in clove (*S. aromaticum*) (Wojdyło et al., 2007). In a similar study, the phenolic compounds of some everyday-use spice plants, such as onion, dill, parsley and celery were identified and quantitatively assessed by HPLC. Chlorogenic acid was reported as the dominant phenolic compound in celery leaves and parsley leaves, and o-hydroxycinnamic acid was dominant in dill (Stankevičius et al., 2010). Shan et al. (2005) also reported the presence of phenolic acids (rosmarinic acid, caffeoyl derivatives), phenolic diterpenes, volatile compounds (carvacrol), flavonoids (catechin) in sweet basil (*O. basilicum* L.), phenolic acids (rosmarinic acid), phenolic diterpenes (carnosic acid), volatile compounds and flavonoids in sage (*S. officinalis* L.), phenolic acids (caffeic acid, rosmarinic acid, caffeoyl derivatives), phenolic diterpenes (carnosic acid, carnosol, epirosmanol), volatile compounds (carvacrol), flavonoids in rosemary (*R. officinalis* L.), phenolic acids (gallic acid, caffeic acid, rosmarinic acid), volatile compounds (thymol), phenolic diterpenes, flavonoids in thyme (*T. vulgaris* L.), phenolic acids (gallic acid), flavonol glucosides, phenolic volatile oils (eugenol, acetyl eugenol), tannins in clove (*Eugenia caryophylata* Thunb.), phenolic volatile oils, phenolic acid (caffeic acid), flavanols (catechin) in nutmeg (*M. fragrans* Houtt) and phenolic acids (caffeic acid, p-coumaric acid, rosmarinic acid, caffeoyl derivatives), volatile compounds, (carvacrol) and flavonoids in oregano (*O. vulgare* L.).

In a similar manner, Hossain et al. (2010) reported the presence of thirty eight (38) phenolic compounds in five Lamiaceae spices: rosemary, oregano, sage, basil and thyme using Liquid chromatography coupled with electron span ionization detector and mass spectrometer (LC-ESI-MS/MS). Twenty (20), twenty six (26), twenty three (23), twenty four (24) and twenty (20) different phenolic compounds were found in rosemary, oregano, sage, basil and thyme, respectively. The structures of some of these phenolic compounds found in spices are as shown in Figure 3.

Antioxidant properties

Several oxygen-free radicals and other reactive oxygen species (ROS), which include free radicals such as superoxide anion radicals (O_2), hydroxyl radicals (OH) and non free-radical species such as hydrogen peroxide (H_2O_2) and singlet oxygen (O_2), may be formed in the human body during the normal cellular metabolism and in the food system in the course of food production and processing (Halliwell and Gutteridge, 1999; Halliwell, 2006; Oboh and Rocha, 2007). These radicals induce lipid peroxidation, thereby causing oxidative damage by oxidizing biomolecules such as proteins, lipids and DNA, leading to cell death, tissue damage and diseases such as atherosclerosis, cancer, emphysema, cirrhosis and arthritis (Kehrer, 1993). They could also result in food deterioration. On the other hand, antioxidant refers to a

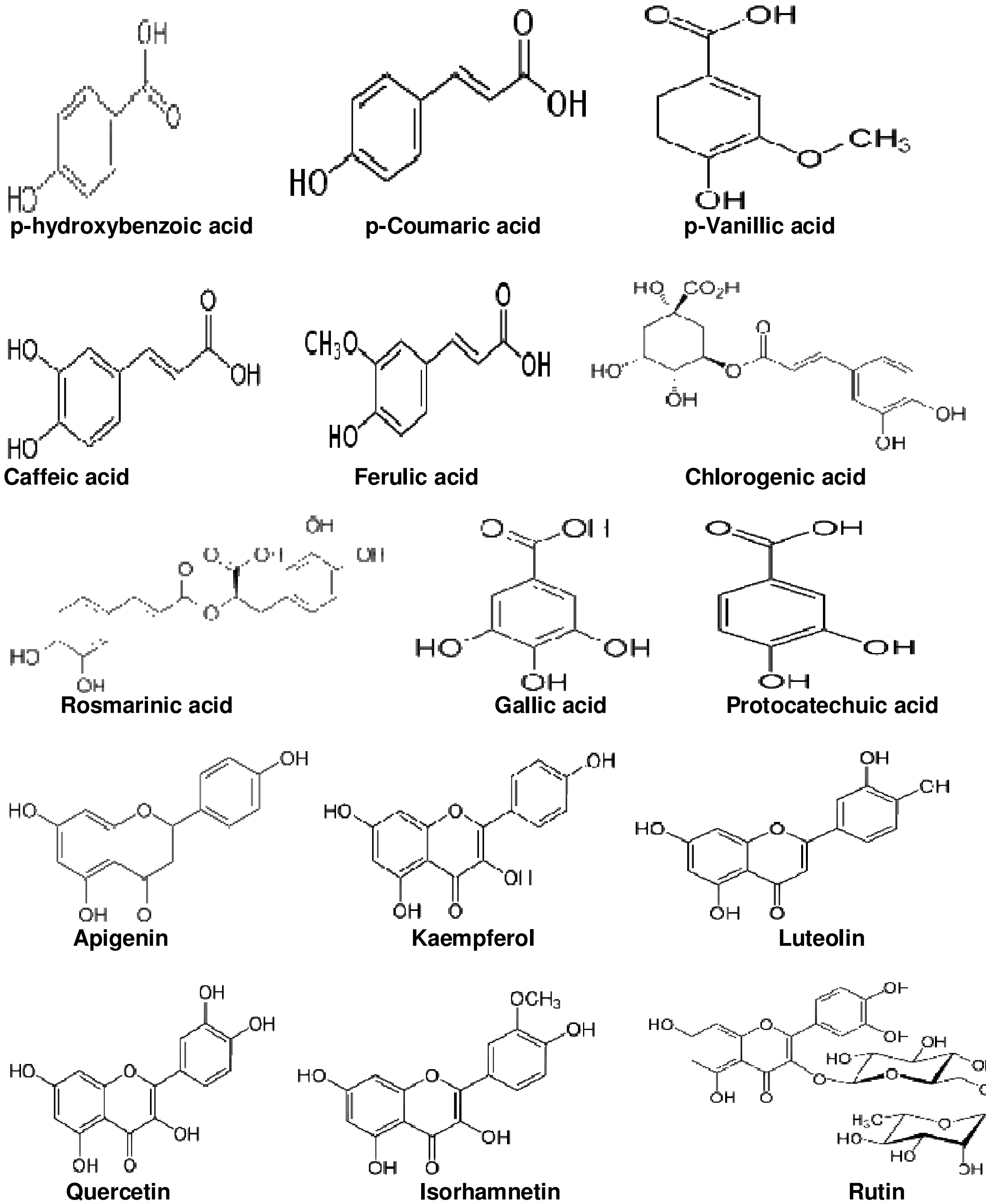

Figure 3. Structure of some phenolic constituents found in some spices.

compound that can delay or inhibit the oxidation of lipids or other molecules by inhibiting the initiation or propagation of oxidative chain reactions, and can thus prevent or repair the damage done to the body's cells by oxygen (Halliwell et al., 1995).

Antioxidants protect by contributing an electron of their own. In so doing, they neutralize free radicals and help prevent cumulative damage to body cells and tissues

(Alia et al., 2003). Much of the total antioxidant activity of plant foods is related to their phenolic content, and not only to their vitamin contents (Chu et al., 2002; Sun et al., 2002; Oboh and Rocha, 2007; Oboh et al., 2008). They exert their antioxidant activity by removing free radicals, chelating metal catalysts, activating antioxidant enzymes, reducing α-tocopherol radicals, and inhibiting oxidases (Amic et al., 2003). Antioxidant may be endogenous or exogenous (can scavenge/deactivate this reactive free radicals, turning them to harmless particles) (Chu et al., 2002). Consumption of antioxidant rich food such as spices, fruits, and vegetables could be a practical approach towards improving antioxidant status, thereby enhancing good health and preventing disease (Chu et al., 2002; Oboh and Rocha, 2007; Carlsen et al., 2010).

Since the antioxidant capacity of plant extracts from different plant foods have been attributed to their high phenolic contents, in the last years, we have assessed the total phenols and flavonoids of different plant foods (Oboh and Rocha, 2007; Adefegha and Oboh, 2011a, 2011b; Oboh et al., 2008, 2010a; 2010b; 2011; 2012a, b, c). The antioxidant properties have also been investigated using several methods: 1,1-diphenyl-2-picrylhydrazine (DPPH) radical scavenging assay (Gyamfi et al., 1999), β-carotene linoleic acid bleaching assay (Pratt, 1980), inhibition of linoleic acid peroxidation (Osawa and Namiki, 1981), ferric reducing antioxidant power (FRAP), total radical trapping antioxidant potential (TRAP) assay (Lissi et al., 1992, 1995), oxygen radical absorbance capacity (ORAC) assay (Cao et al., 1993), 15-lipoxygenase inhibition (Lyckander and Malterud, 1992), lipid peroxidation (LPO) method (Ohkawa et al., 1979), nitro blue tetrazolium (NBT) reduction assay or superoxide anion scavenging activity (Beauchamp and Fridovich, 1971), hydroxyl radical scavenging activity (Halliwell et al., 1987), hydrogen peroxide scavenging activity (Ruch et al., 1989), 2,2-azinobis-(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical scavenging method (Re et al., 1999), reducing power assay (Oyaizu, 1986), ammonium thiocyanate (ATC) assay method (Masude et al., 1992) and ferric thiocyanate (FTC) method (Mitsuda et al., 1996).

In a number of studies, spices from different botanical families, such as Myristicaceae (for example nutmeg), Zingiberaceae (for example, ginger, galangal alligator pepper and bastered melegueta), Lamiaceae (for example, sweet basil, thyme, rosemary, oregano, and sage), Lauraceae (for example, cinnamon), Piperaceae (for example, black pepper, white pepper), Myrtaceae (for example, clove), Solanaceae (for example, chili pepper) and Umbelliferae (for example, Fennel, cumin, and *Angelica dahurica*), have been assessed for their antioxidant properties using some of the aforementioned assay methods (Zheng and Wang, 2001; Shan et al., 2005; Oboh et al., 2010b; Lu et al., 2011; Adefegha and Oboh, 2011b). Reports revealed that these spices possess moderate and high antioxidant activity (Shan et al., 2005; Lu et al., 2011; Adefegha and Oboh, 2011b).

Previous studies have shown that these spices are rich in phenols and flavonoids, hence their disease preventing and health promoting abilities have been attributed to the presence of these phytochemicals (Fasoyiro et al., 2006; Olonisakin et al., 2006; Wojdyło et al., 2007; Uwakwe and Nwaoguikpe, 2008; Ezekwesili et al., 2010; Doherty et al., 2010). Several studies have also correlated antioxidant capacity with total phenolic content of legumes, vegetables, pepper, spices, medicinal herbs and other plant foods (Oboh, 2006; Oboh and Rocha, 2007; Oboh et al., 2008, 2011; Oboh and Ogunruku, 2010; Adefegha and Oboh, 2011b; Oboh and Ademosun, 2011). These reports may validate the claims that phenolic compounds are responsible for most of the antioxidant effects in plants (Pietta, 2000; Chu et al., 2002; Sun et al., 2002; Cai et al., 2004; Liu et al., 2008; Shan et al., 2005; Odukoya et al., 2005; Oboh and Rocha, 2007).

Our report on the phenolic content and antioxidant properties of aqueous extract of some Nigerian spices: *M. myristica* (Africa nutmeg), *X. aethiopica* (Ethiopian pepper), *S. aromaticum* (tropical cloves), *P. guineense* (Black pepper), *A. danielli* (bastered melegueta), *A. melegueta* (alligator pepper/grains of paradise) and *Clerodendrum volubile* (Locally known as "Obenetete")] indicated that the total phenol content of the spices range from 0.6 (*M. myristica*) to 2.28 mg gallic acid equivalents per g (mg GAE/g) (*A. melegueta*). In the same vein, *A. melegueta* (0.55 mg GAE/g) was reported to have the highest flavonoid content, followed *Clerodendrum volubible* (0.52 mg GAE/g), *P. guineense* (0.41 mg GAE/g), and *Aframomum danielli* (0.29 mg GAE/g), *Syzygium aromaticum* (0.26 mg GAE/g), *Xylopia aethiopica* (0.24 mg GAE/g) and *Monodora myristica* (0.21 mg GAE/g) (Adefegha and Oboh, 2011a).

Furthermore, the spice extracts also showed interesting antioxidant properties as typified by their ferric reducing antioxidant property, Fe^{2+}-chelating ability, inhibition of Fe^{2+}/H_2O_2-induced decomposition of deoxyribose and inhibition of Fe^{2+}-induced lipid peroxidation in rat's brain (Adefegha and Oboh, 2011a). Shan et al. (2005) reported the phenolic contents and total antioxidant capacity of 26 spices by assessing the ability of their extracts to scavenge free radicals using the ABTS model. The ABTS radical scavenging activity of the spice extracts ranged from 0.55 (poppy) to 168.7 mmol trolox equivalents antioxidant capacity per 100 g (TEAC/100 g) dry weight (clove). Also, the total phenol content of the spices was reported to range from 0.04 to 14.38 g of gallic equivalents per 100 g (GAE/100 g) of dry weight (DW). Hence, positive correlation between the total phenol contents and the total antioxidant capacity was observed in the spices (Shan et al., 2005; Adefegha and Oboh, 2011a).

In another study where the antioxidant properties of 30 spices was assessed using FRAP, ABTS radical scavenging ability and microsomal lipid peroxidation

(MLP) assays (Hossain et al., 2008). It was reported that clove exhibited the highest ABTS radical scavenging ability, FRAP and anti-radical powers (ARP) on microsomal lipid peroxidation. Rosmarinic acid and eugenol, commonly found in clove was reported to possess higher antioxidant capacities than that of the synthetic antioxidants tested (Hossain et al., 2008). This could be an indication that natural antioxidants from spices might have more beneficial roles than the synthetic ones aside the advantage of being a safe alternative. Oxidative damage by free radicals has been implicated in the pathogenesis of vascular disease in diabetic complications, and several studies have revealed that antioxidants can attenuate these oxidative stress-induced changes in diabetes and hypertension (Ceriello, 2003; Vasdev et al., 2006). In an animal study carried out by Drobiova and his colleagues, garlic was reported to elevate serum antioxidant levels, decrease serum glucose in the garlic-treated diabetic rats and reduce systolic blood pressure in the garlic-treated hypertensive rats (Drobiova et al., 2010).

Inhibition of key enzymes linked to type-2 diabetes

Diabetes is one of the leading threats to worldwide public health and a major cause of global death (WHO, 1999). Reports mentioned that the number of people suffering from diabetes is about 171 million and this was projected to increase in geometric proportion to 366 million by 2030 (Wild et al., 2004). In all cases of diabetes, development of one or more complicated chronic diseases such as neuropathy, retinopathy, nephropathy and cardiomyopathy is common. There are two types of diabetes: type 1 and 2. Type 2 is more prevalent than type 1, and more than 90% of diabetes cases are that of the T2D.

T2D may be regarded as the second most common non communicable disorder, after hypertension in terms of public health significance (WHO, 1999). T2D is a metabolic disorder characterized by hyperglycemia, insulin resistance, insulin secretion and beta-cell dysfunction (WHO, 1999). There is growing scientific evidences that excess generation of highly reactive free radicals, largely due to hyperglycemia, cause oxidative stress, which further elevates the development and progression of diabetic complications (Johansen et al., 2005). Consequences of oxidative stress are damage to DNA, lipids, proteins, disruption in cellular homeostasis and accumulation of damaged molecules (Jakus, 2000). Oxidative stress is increased in diabetes because of multiple factors. These factors include glucose auto-oxidation, protein glycation, binding of advanced glycation end products (AGEs) to their receptors, oxidation/reduction imbalances, and reduction in antioxidant defenses can lead to increased free radical production (Penckofer et al., 2002; Rahimi et al., 2005).

The use of natural antioxidants as a complementary therapeutic approach in the management of diabetes is on the increase (Srinivasan, 2005b; Golbidi et al., 2011). Curcumin and turmeric were reported to be effective against the development of diabetic complication in rat's eyes (Suryanarayana et al., 2005), and turmeric was reported to reduce blood sugar level and modulate polyol pathway in diabetic albino rats (Arun and Nalini, 2002). In another study, curcumin, an active principle of turmeric, was reported to ameliorate diabetic nephropathy in streptozotocin-induced diabetic rats (Sharma et al., 2006). Supplementation of turmeric was also shown to attenuate proteinuria, TGF-β and IL-8 in patients with overt type 2 diabetic nephropathy and can be administered as a safe adjuvant therapy for these patients (Khajehdehi et al., 2011).

Administration of turmeric or curcumin was also reported to attenuate alloxan-induced diabetes in experimental rats (Arun and Nalini, 2002). Cinnamon is another spice that is known for its multiple health benefits. Available *in vitro*, *in vivo* and clinical evidences have indicated hypoglycaemic activity of cinnamon (Khan et al., 2003; Pham et al., 2007; Bandara et al., 2012). Although, several synthetic drugs have been developed to manage T2D but they come with their attendant side effects and are expensive. In recent times, investigations are being carried out to source natural and cheap plant foods for managing T2D and its complication through the consumption of food rich in spices, vegetables, legumes and fruits (Shim et al., 2003; Kwon et al., 2007; Ranilla et al., 2010; Oboh et al., 2010b).

Many studies have shown that inhibition of key enzymes (α- amylase and α-glucosidase) relevant to T2D could serve as therapeutic approach to the management of this disease, and some vital bioactive compounds such as polyphenols that possess interesting structure-function benefits have shown promising potentials (McCue et al., 2005; McDougall et al., 2005). α-Glucosidase and α-amylase are the key enzymes involved in the digestion of carbohydrates (McCue et al., 2005; Ali et al., 2006). α-Amylase degrades complex dietary carbohydrates to oligosaccharides and disaccharides that are ultimately converted into monosaccharides by α-glucosidase (Figure 4). Liberated glucose is then absorbed by the gut and results in postprandial hyperglycemia (Kim et al., 2000; Shim et al., 2003). The inhibition of enzymes involved in the digestion of carbohydrates can significantly decrease the postprandial increase of blood glucose after a mixed carbohydrate diet by delaying the process of carbohydrate hydrolysis and absorption (Kwon et al., 2006; Oboh et al., 2010b).

The control of postprandial hyperglycemia is an important strategy in the management of diabetes mellitus, especially T2D, and reducing chronic complications associated with the disease (Kim et al., 2000; Ali et al., 2006). This is done by retarding the absorption of glucose through the inhibition of the carbohydrate-hydrolysing enzymes α-glucosidase and α-amylase in the digestive

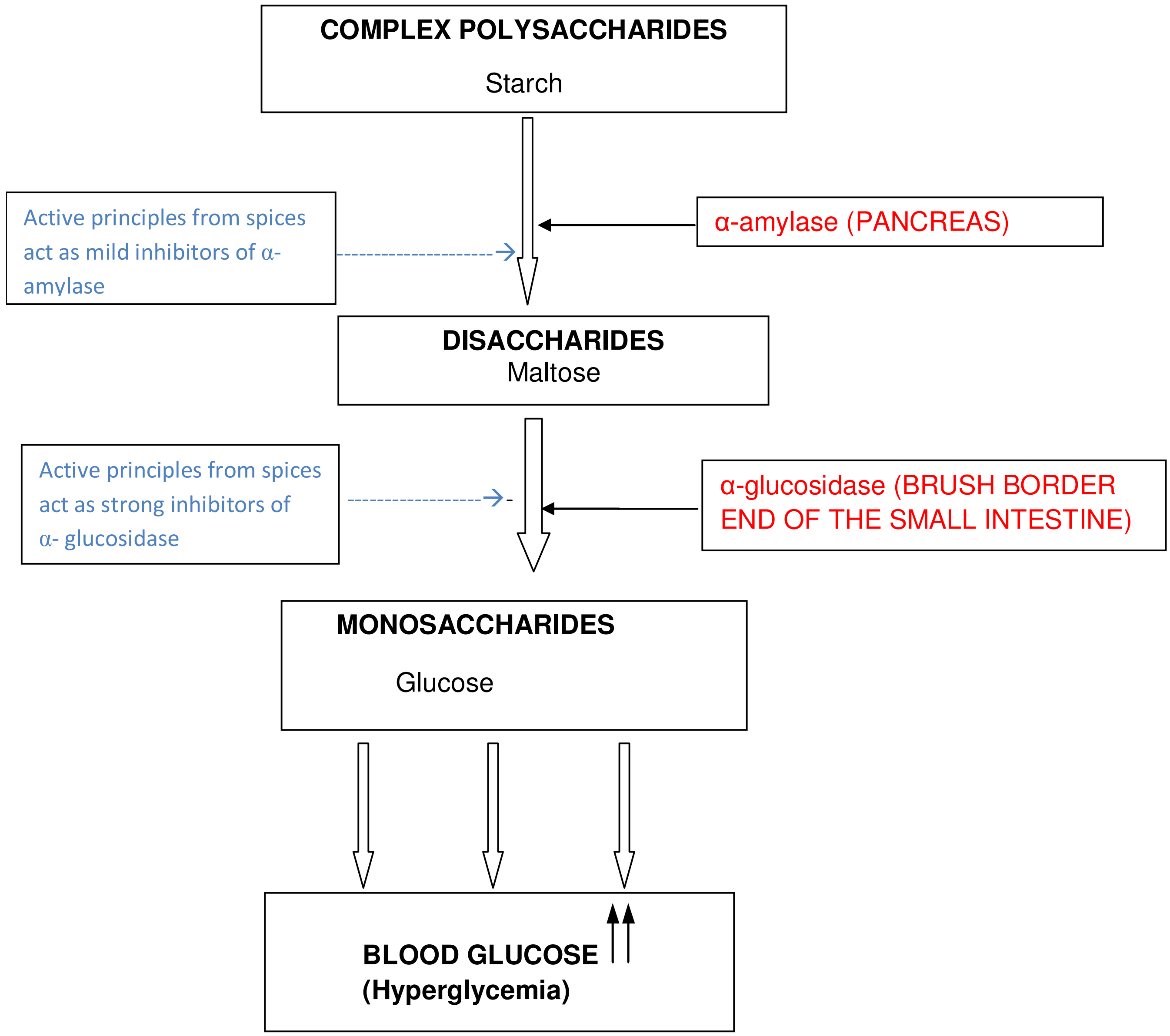

Figure 4. Schematic diagram showing the actions of α- amylase and α- glucosidase in starch digestion.

tract (Kim et al., 2000; Shim et al., 2003; Oboh et al., 2010b). Inhibitors of these enzymes could cause delay in carbohydrate digestion, prolong overall carbohydrate digestion time, causing a reduction in the rate of glucose absorption and consequently blunting the postprandial plasma glucose rise (Bhadari et al., 2008).

Several drugs such as acarbose, miglitol, voglibose, nojirimycin and 1-deoxynojirimycin have been developed and are currently in use. These drugs could act by either blocking or inhibiting these enzymes, however, they come with financial constraints and their attendant side effects, hence, alternative treatments need to be evaluated. Therefore, effective, nontoxic and cheap natural dietary inhibitors of α-amylase and α-glucosidase with little or no side effects could be potentially promising and highly desirable. Moreover, there are strong evidences that dietary factors could be involved in the regulation and prevention of T2D (Kwon et al., 2007). Several medicinal plant and plant foods have been shown to exert their antihyperglycemic activity via inhibition of carbohydrate hydrolyzing enzymes (Ortiz-Andrade et al., 2005; McDougall et al., 2005; Cheplick et al., 2007; Oboh et al., 2010b; Pinto et al., 2010; Ranilla et al., 2010).

α-Glucosidase and α-amylase inhibitors, which interfere with enzyme activity in the brush-border of the small intestine, could slow the liberation of D-glucose from oligosaccharide and disaccharides, resulting in delaying glucose absorption and decreasing postprandial glucose levels. The toxicity of α-glucosidase and α-amylase inhibitors of natural source is much lower than that of the synthetic inhibitors. Kwon et al. (2007) reported that pepper varieties possess high antioxidant and good inhibitory profile on carbohydrate-degrading enzyme such as α-glucosidase related to glucose absorption. Green pepper and long hot pepper had little or no inhibitory effect on the α-amylase activity, which revealed their potential use with reduced side effects.

In our laboratory, two varieties of ginger were reported to show mild inhibition of α-amylase and strong inhibition of α-glucosidase, this suggest their potential use in nutritional intervention in the management or control of postprandial hyperglycemia associated with T2D. White ginger showed more promising attributes than red ginger (Oboh et al., 2010b). Nickavar and Yousefian (2009) investigated the inhibitory effects of six *Allium* spp. on α-amylase activity, and four of the selected *Allium* spp. were reported to show appreciable α-amylase inhibition. In another study, some Cameroonian spices namely, *A. daniellii, Hypodapnis zenkeri, Echinops giganteus, A. citratum, X. aethiopica* and *Scorodophloeus zenkeri* were demonstrated to have anti-amylase and anti-lipase activities, as well as good antioxidant potentials (Etoundi et al., 2010). Cazzola et al. (2011) also reported that spices such as sage, rosemary, basil, parsley, chili, garlic and onion have interesting inhibitory activities on lipid peroxidation, α-glucosidase and α-amylase.

Furthermore, our recent report also revealed the inhibitory effects of some tropical spices: *X. aethiopica* [Dun.] A. (Ethiopian pepper), *M. myristica* (Gaertn.) Dunal (nutmeg), *S. aromaticum* [L.] Merr. et Perry (clove), *P. guineense* Schumach. et Thonn (ashanti pepper), *A. danielli* K. Schum (bastered melegueta) and *A. melegueta* (Rosc.) K. Schum (alligator pepper) on α-amylase, α-glucosidase and sodium-nitroprusside (SNP)-induced lipid peroxidation in pancreas (Adefegha and Oboh, 2012a). The anti-diabetic properties of the spices were attributed to the presence of biologically active phytochemicals such as phenolic constituents of the spices. Enzyme inhibition, free radical scavenging ability and prevention of lipid peroxidation may be part of the possible mechanism of action of the spices, and this might have accounted for their usage in folklore medicine as antidiabetic gents (Oboh et al., 2010b; Adefegha and Oboh, 2012a).

In a similar manner, Ranilla et al. (2010) also reported that high phenolic and antioxidant activity-linked spices (Huacatay, *Tagetes minuta* and Guascas, *Galinsoga parviflora*), and medicinal plants (Chancapiedra, *Phyllantus niruri* L. and Zarzaparrilla, *Smilax officinalis*), and herbal teas (Yerba Mate, *Ilex paraguayensis* St-Hil) in Latin America, have strong α-glucosidase inhibitory potential with no inhibition against porcine pancreatic α-amylase *in vitro*. Furthermore, Cat's claw (*Uncaria tomentosa*), cinnamon (*Cinnamomum zeylanicum* B.), Linden tea Tilo (*Tilia platyphyllos*) and Boldo (*Peumus boldus*) were reported to strongly inhibit both α-glucosidase and α-amylase enzymes. In a related study, phenolic-rich (free and bound) extracts from clove buds also showed interesting inhibitory properties against α-glucosidase (Adefegha and Oboh, 2012b).

Ye et al. (2010) reported that some plant constituents commonly used in traditional Chinese medicine for the treatment of diabetes mellitus possess interesting inhibitory activities on α-amylase and α-glucosidase. These plant constituents are ginsenoside, puerarin, dioscin, genistein, quercetin, chlorogenic acid, taraxasterol, kaemferol, betulinic acid and paeonol from some traditional Chinese medicinal plants, and spices for treating diabetes mellitus (*Panax ginseng, P. notoginseng, Puerariae lobata, Dioscorea opposite, Astragalus membranareus, Phaseolus calcaratus Gynostemma pentaphyllum, Lonicera japonica, Paeonia lactiflora, Ophiopogon japonicas, Taraxacum mongolicum, Bupleurum chinense, Ziziphus jujuba var. spinosa*) showed strong inhibitory activities on both α-glucosidase and α-amylase (Ye et al., 2010).

Inhibition of angiotensin-I converting enzyme

Cardiovascular complications, characterized by endothelial dysfunction and accelerated atherosclerosis, are the leading cause of morbidity and mortality associated with diabetes (Johansen et al., 2005). Hypertension is one of the commonest cardiovascular diseases which have become a global epidemic affecting 15 to 20% of all adult population (Miguel et al., 2007). Hypertension means persistent increase in blood pressure (BP). According to WHO, the normal BP for an individual should be 120/80 mmHg and if it exceeds 140/90 mmHg, it is classified as 'high BP', otherwise known as hypertension. Hyperglycemia resulting from T2D may lead to hypertension; a common cardiovascular disease.

The rennin-angiotensin system (RAS) plays a key role in the regulation of blood pressure regulation in humans (Coates, 2003). Renin produces angiotensin-I, an inactive decapeptide from angiotensinogen, after which it is cleaved by angiotensin-I converting enzyme (ACE) to release a potent vasoconstrictor angiotensin-II, an octapeptide (Je et al., 2009). ACE degrades bradykinin, a vasodilator in blood vessels, and stimulates the release of aldosterone in the adrenal cortex. The ACE activity is directly linked to hypertension, as angiotensin-II is the blood pressure regulating hormone. Increased ACE activity has been linked to narrowing of lumen of blood vessels, which results in increased blood pressure (Figure 5). Therefore, inhibition of ACE activity may provide a major anti-hypertension benefits by effectively lowering hypertension (Je et al., 2009).

Synthetic ACE inhibitors such as captopril, lisinopril,

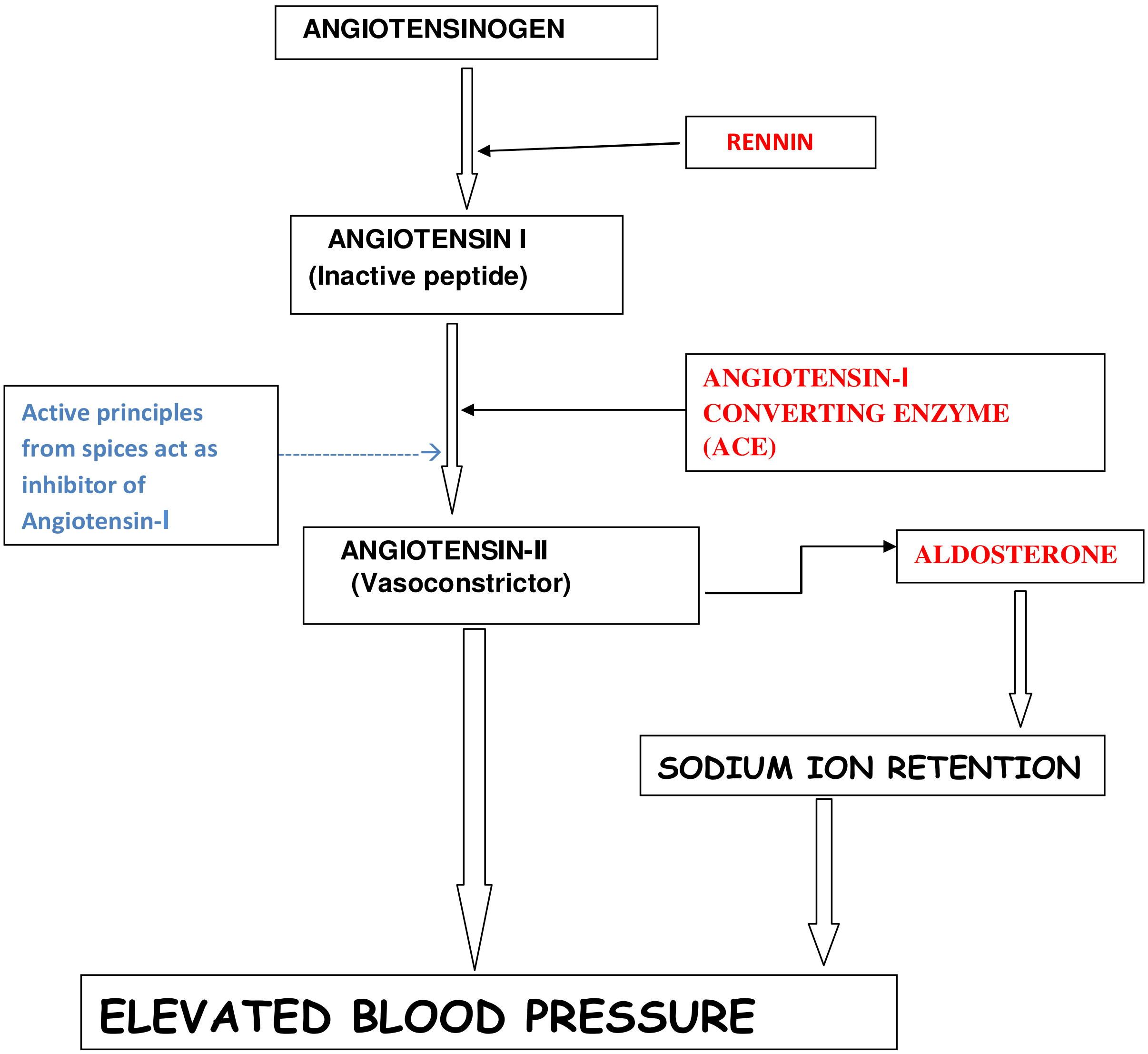

Figure 5. Schematic diagram showing the action of angiotensin-1 converting enzyme in rennin-angiotensin system.

enalapril, fosinopril and ramepril are currently in use and have shown to be very successful in controlling high blood pressure (Campos et al., 2010). They exert their antihypertensive effect by competiting for the same active site of ACE. Moreover, these drugs come with their financial constraints and their side effects such as cough, taste alterations and skin rashes. This has prompted the search for naturally-occurring ACE inhibitors, especially in flavonoids and peptides rich foods. There are indications that they are safer and lower-cost alternatives when compared to synthetic drugs (Je et al., 2009; Campos et al., 2010). Reports have shown the antihypertensive potentials and cardiovascular benefits of some medicinal plants and plant foods (Schmeda-Hirschmann et al., 1992; Hansen et al., 1995; Je et al., 2009; Pinto et al., 2009; Oboh and Ademosun, 2011; Ademiluyi and Oboh, 2012; Oboh et al., 2012c).

Ginger (*Z. officinale*) and red pepper (*Capsicum annum*) have been shown to possess high ACE inhibitory properties and could serve as dietary means of hypertension management (Ranilla et al., 2010). Clinical evidence has shown that garlic can reduce the diastolic blood pressure in hypertensive patients (McMahon and Vargas, 1993). In related study carried out to compare the cardioprotective properties of freshly crushed and processed garlic (Mukherjee et al., 2009), the authors discovered that both freshly crushed garlic and processed garlic provide cardioprotection, although the freshly crushed garlic showed a better potentials. In another clinical trial, cardamom was shown to effectively reduce blood pressure, enhance fibrinolysis and improve antioxidant status, without significantly altering blood lipids and fibrinogen levels in hypertensive patients (Verma et al., 2009).

Hypocholesteroleamic effect

Hypercholesterolemia, otherwise known as high blood cholesterol, is a major risk factor for the development of atherosclerosis and occlusive vascular disorders (Levy and Brink, 2005). WHO reported that hypercholesterolemia accounts for 18 and 56% of the world's population suffering from cerebrovascular disease and ischemic heart disease, respectively (WHO, 2002). Therapeutic life styles such as low saturated fat and cholesterol diet, weight management, and increased physical activity are vital for blood cholesterol regulation. Scientific evidences from several animal models revealed that curcumin from turmeric and capsaicin from red pepper are potent hypocholesterolaemic and hypolipidemic agents (Kempaiah and Srinivasan, 2002, 2004; Srinivasan et al., 2004).

Commercially available drugs such as statins are presently used for blood cholesterol reduction in people with or at cardiovascular risk nowadays (Endo, 2004; Kapur et al., 2008). The drug, statin, acts by the inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase, (HMG-CoA reductase). HMG-CoA reductase is the rate limiting enzyme that catalyzes the reduction of HMG-CoA to mevalonate and provides feedback regulation of cholesterol synthesis in cells (Brown and Goldstein, 1980). Several *in vitro* and *in vivo* studies have shown HMG-CoA reductase inhibitory effects of natural plant products. In an animal model, garlic supplemented diets was reported to reduce hepatic cholesterol synthesis by the inhibition of HMG-CoA reductase (Qureshi et al., 1987). Allicin, an organosulfur compound found in spice garlic (*A. sativum*) was reported to inhibit HMG-CoA reductase in both rat hepatocytes and HepG2 cells (Gebhardt et al., 1994; Gebhardt and Beck, 1996). β-Sitosterol from black cumin seeds was found to suppress hepatic HMG-CoA reductase activity in rats (Gylling and Miettinen, 2005). Curcumin from turmeric was also reported to decrease liver enzyme in cholesterol fed rats (Murugan and Pari, 2006). Quercetin, a bioflavonoid found in the skins of red onions, significantly lowers this liver enzyme in high cholesterol fed rats (Bok et al., 2002).

CONCLUSION AND RECOMMENDATION

Consumption of spice-rich foods and their ingredients could be a more effective strategy towards the management of DM and hypertension. The advantages of spice-rich food and spice antioxidant could be associated with high compliance and absence of side effects. Spice rich foods and spice antioxidant may exert their actions by possible inhibition of key enzymes linked to TY2DM (α- amylase and α-glucosidase), hypertension (ACE) and hypercholesterolaemia (HMG-CoA reductase). Spice phenolics may also serve as potential hurdles to counter the complications of diabetes arising from oxidative dysfunction. Spices have been shown to possess good nutrient benefits with low calories, possess good inhibitory profiles on carbohydrate-modulating enzymes, ACE and HMG-CoA reductase, which correlates to their total phenolic contents, phenolic profile and antioxidant properties. This review points out the potential of spices, especially from the tropics for both T2D-linked hyperglycemia, hypertension and hypercholesterolaemia management. It also projects spice based diets as an effective dietary strategies for controlling early stages of postprandial hyperglycemia and associated hypertension. Overall, this review provides the biochemical rationale for further animal and clinical studies.

Due to the increased incidence and prevalence of several degenerative diseases such as diabetes, cardiovascular diseases including hypertension, cancer and neurodegenerative diseases including Alzheimer's diseases, concomitant drug resistance actions to these diseases and their attendant side effects, we therefore recommend an alternative dietary therapy via increased consumption of whole spice meal and spice-rich food. In a nutshell, we say "Spice up your life". This assertion supports what the great philosopher Hippocrates said about food "you are what you eat".

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