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Bifunctional Antidiabetic - Anticancer Dual - Active Phytochemicals: Adjuncts or Alternatives to Conventional Therapies

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Abstract

Plants owe their various pharmacological properties to their active phytochemical components. Phytochemicals are bioactive chemicals or secondary metabolites products of plants, which play important roles in plant defense mechanisms.

The major groups of these compounds, also known to be very protective in humans and animals, include phytosterols, flavonoids, terpenoids, saponins, alkaloids, carotenoids, aromatic acids, organic acids, essential oils and protease inhibitors.

These phytochemicals have demonstrated significant antioxidant activities through scavenging free radicals, quenching ROS, and inhibiting oxidative enzymes. They play important roles against the initiation, formation and sustenance of oxidative stress.

Apart from their roles in oxidative stress, some phytochemicals are known to have direct specific antidiabetic and anticancer activities, and modulate the signal transduction pathways common to both diseases.

The aim of this review is to describe the antidiabetic and anticancer dual-roles of these phytochemicals, and highlight their importance in the management of diabetic patients with concurrent cancer illness and cancer patients with glucose intolerance. This review equally aims to compare the intended use of these phytochemicals as adjuncts or alternatives to conventional antidiabetics and anticancer agents.

Keywords: Antidiabetic-Anticancer, Dual-Active Phytochemicals, Monotherapy, Adjuncts.

1. Introduction

There is increasing knowledge today about the role of oxidative stress in the pathology of many chronic illness like diabetes and cancer. Oxidative stress results from imbalance between reactive oxygen species (ROS) prooxidant formation and their elimination or neutralization. Oxidative stress is initiated by free radicals. These achieve stability via electron pairing with biological macromolecules like proteins, lipids, and DNA in normal human cells and cause protein and DNA damage with lipid peroxidation. These changes progress to cancer, diabetes, atherosclerosis, inflammatory diseases, aging etc [1,2].

Plants have their various pharmacological properties due to their active phytochemical components. Phytochemicals are bioactive chemicals or secondary metabolites products of plants which are non-nutritive but very important in protecting plants from microorganisms, insects and unfavorable environmental changes. The major groups of these phytochemicals, also known to be very protective in human and animals, include phytosterols, flavonoids, terpenoids, saponins, alkaloids, carotenoids, aromatic acids, organic acids, essential oils and protease inhibitors [3]. These phytochemicals have demonstrated significant antioxidant activities through scavenging free radicals, quenching ROS, and inhibiting oxidative enzymes and play important roles against the initiation, formation and sustenance of oxidative stress and reactive oxygen species in diabetes and cancer which have oxidative stress as a common underlying pathology [2].

Apart from their roles in oxidative stress, some plants (phytochemicals) are known to have direct specific antidiabetic and anticancer activities. Studies have evaluated the effectiveness of plant-based inhibitors of α-amylase and α-glucosidase inhibitors as well as their antioxidant activity using half inhibitory concentration IC50 (for enzyme inhibition) and half effective concentration EC50 (for antioxidant activity) parameters [4]. Ethanol and Hexane extracts of plants inhibited digestive amylase and lipase with more than 70% antioxidant and antiglycation properties [5].

Studies investigating chemopreventive roles of natural phytochemicals to prevent, impede, delay or cure cancer, showed that these agents interact with important cancer signal transduction pathways like p38 MAPK, PI3K/Akt/ mTOR, NF-kB, cyclin D1, c-myc and apoptosis pathways. These agents equally act on chromatin remodeling during DNA damage, DNA methylation, microRNAs, cyclooxygenases-2 (COX-2) involved in inflammation mediation, Histone modification etc [6].

The aim of this review is to describe the antidiabetic and anticancer dual-roles of these phytochemicals and highlight their importance in the management of diabetic patients with concurrent cancer illness and cancer patients with glucose intolerance. This review equally compared their intended use as adjuncts or alternatives to conventional antidiabetics and anticancer agents.

2. Phytochemicals and Phytonutrients Roles in Diabetes and Cancer

A) Phenols: examples are flavonoids, phenolic acid, stilbenes and lignans.

1. Flavonoids: these are large class (with over 6,000 members) of variable phenolic structures found in fruits, vegetables, grains, barks, roots, stem, flowers, tea and wine. The 6 major subgroups are flavonols, flavanols (catechins), flavones, flavanones, isoflavones and anthocyanins. The various subgroups of flavonoids are antioxidant and protect against free radical injuries and damage through various mechanisms. Because of the high reactivity of flavonoids hydroxyl group, free radicals are rendered inactive as shown in Korkina and Afanasev equation Flavonoid (OH) + R● → Flavonoid (O●) +RH where R● is the free radical and O● is the oxygen free radical [7]. Flavonoids are commonly referred to as vitamin P.

a) Flavonols: found mainly in lettuce, grapes, onions, kale berries. The family consist of:

Quercetin: is the most abundant flavonoid in human diet. Quercetin reduces plasma glucose levels at doses of 10, 25 and 50 mg/kg of body weight in animal studies [8]. Antidiabetic effects of quercetin includes among others: decreasing of lipid peroxidation, glucose absorption by GLUT 2 and inhibition of insulin dependent activation of Phosphoinositide 3-kinases (PI3K) [9] [10].The anticancer properties of quercetin involve targeting molecular pathways involved glucose metabolism and mitochondrial function, its ability to enhance cell viability loss, apoptosis and autophagy via regulation of PISK/Akt/mTOR, Wnt/catenin and MAPK/ERK 1/ 2 pathways [11].

Rutin: glycosylated quercetin extracted from plants such as oranges, lime, lemon and grapes. Rutin decreases the carbohydrates absorption, increase gucose uptake, decrease tissue gluconeogenesis, activates insulin secretion. Rutin equally decreases reactive oxygen formation, advanced glycation end products precursors, sorbitol and pro-inflammatory cytokines [9]. Administration of 50mg/kg or 100mg.kg rutin to streptozotocin (STZ) model type 1 diabetic rats very much decreased HbA1c and FBS [12]. Anticancer effects of rutin are mediated through regulation of different cellular signaling pathways like Wnt/β-catenin, p53, PI3K.Akt, JAK/STAT, MAPK, apoptosis, NF-Kb pathways [13].

Kaempferol: kaempferol in vitro treatment enhanced viability, inhibited apoptosis and decreased caspase-3 activity in β-cell in human islets exposed chronically to hyperglycemic condition. These favorable effects are linked to enhanced cAMP signaling, antiapoptotic Akt and Bcl-2 protein expression, insulin secretion and synthesis in β-cells [14]. Kaempferol acts on several intracellular and extracellular targets that are involved in cell signaling pathways which then modulate cancer proliferation like apoptosis, cell cycle, invasion, metastasis, angiogenesis and inflammation [15].

Isorhamnetin: A monomethoxyflavonol found in vegetables and fruits. It is tyrosinase inhibitor, an antitumor agent and peroxisome proliferator – activated receptor antagonist. It is effective against breast cancer by targeting several molecular pathways like Akt/mTOR/MAPKs, inhibits cell proliferation and enhances apoptosis [16]. Isorhamnetin antioxidant property was found to be comparable to that of ascorbic acid and butylated hydroxytoluene and the linear correlations were significant in the antioxidant assays [17].

High fat diet and Streptozotocin induced diabetic mice were treated orally with isorhamnetin (10mg/kg) or metformin (200mg/kg) for 10days, results showed that isorhamnetin decreased elevated serum glucose, fasting glucose, LDL, triglyceride, cholesterol, homeostasis model assessment of insulin resistance (HOMA-IR), MDA, IL-6, GSSG and increased GSH in treated diabetic group compared to vehicle control [18]. Isorhamnetin inhibited the proliferation of from human colorectal cancer cell lines HT-29, HCT116 and SW480, induced sell cycle arrest at the G2/M phase and inhibited cell proliferation by blocking the PI3K-Akt-mTOR pathway [19].

Fisetin: is a dietary flavonol found in several fruits and vegetables like strawberry. Apples, onions, tomatoes and grapes. It is a potent antioxidant, anti-inflammatory, memory enhancer and anti-aging. It has powerful senolytic and senotherapeutic properties that promotes longevity by killing senescent cells that drives aging and diseases in human and mice Fisetin inhibited human LDL oxidation in vitro, it induced quinone oxidoreductase activity in murine hepatoma 1c1c7 cells in time and dose dependent manner which was linked with increased mRNA expression. Fisetin also increased intracellular glutathione (GSH) levels and metabolism in mouse hippocampal HT-22 cells, thereby protecting them from glutamate which reduces GSH level [20].

Fisetin at oral dose of 10mg/kg given to diabetic rats reduced blood glucose and glycosylated hemoglobin levels and increased plasma insulin level, with reduction of lipid peroxides and hydroperoxides [21]. Fisetin anticancer properties have been reported in several in vitro and in vivo researches. Fisetin affect various signal pathways like inhibiting PI3K/Akt/mTOR signaling, MAPK and NF-kB. It induces apoptosis in in many cancer cells by blocking cyclooxygenase – 2, Wnt/EGFR/NF-kB pathways and activating caspase -3 and caspase -8/caspase -3 pathways through ERK1/2 [22].

Morin: morin is a dietary bioflavonoid originally isolated from groups in moraceae family, but found in leaves, fruits, stems and branches of various medicinal plants. It has potent antioxidant, antidiabetic, anti-inflammatory, anticancer, antibacterial properties.

30mg/kg body weight of morin administered orally reduced blood ammonia, lipid peroxidation, oxidative stress and increased antioxidant levels in ammonia chloride-induced (100mg/kg) hyperammonemic rats [23]. 40mg/kg of morin was used to pre-treat male albino rats daily for 30days. Myocardial ischemia was induced by 85mg/kg of isoproterenol (ISO) injected into the rats at interval of 24hours for 2 days. The animals were divided into 4 groups: a. control, b. morin treated, c. ISO control and d. Pretreated rats followed by ISO. Results showed that ISO elevated thiobarbituric acid reactive substances (TBARS) and lipid hydroperoxide (LOOH) in plasma and heart, but pretreatment with morin significantly decreases these changes to normal. Morin equally significantly increases the activities of the antioxidant enzymes glutathione peroxidase and glutathione-s-transferase and the levels of reduced glutathione in opposition to ISO [24].

Studies carried out with protein tyrosine phosphatase 1B (PTP1B) – deficient mice revealed that PTP1B is the major negative regulator of insulin signaling. Inhibition or down regulation of this enzyme leads to increased insulin sensitivity. Morin was selected from the group of polyphenolic compounds as PTP1B inhibitor after screening their activity. Morin was shown to: be a non-competitive inhibitor of PTP1B, enhance the phosphorylation of insulin receptor and Akt, inhibit gluconeogenesis and promotes glycogen synthesis [25].

Morin anticancer properties are via many chemopreventive effects like decreasing oxidative stress, phase II enzymes activation, apoptosis induction, downregulation of p-Akt and NF-Kb expression and involvement in other signal transduction pathways like STAT 3, PI3K/Akt, MAPK and Hippo pathways [26]. Morin (150-200μM) prevented EGF- induced metastatic potential and inhibited cell migration and MMP-9 activity by inhibiting the EGFR signaling pathway in SK-BR-3 cells. Morin – induced decrease in cell viability was linked to inhibition of HER2/EGFR signaling pathway [27].

b) Flavanones: is one of the 6 subclasses of flavonoids found in several plant species and citrus fruits. The family consist of:

Hesperidin: is a bioflavonoid found mainly in citrus fruits. Upon ingestion, hesperidin is broken down to its aglycone, hesperetin.

Hesperidin (Hsd) and its aglycone, hesperetin (Hst), have many pharmacological effects especially antioxidant and anti – inflammatory [28,29]. The antioxidant of both hesperidin and hesperetin include radical scavenging of intracellular reactive oxygens species (ROS), up-regulating natural antioxidant defense system like glutathione and enhancing antioxidant cellular defenses through the ERK/Nrf2 signal pathway [29,30].

Streptozotocin (STZ) induced diabetic rats had significantly reduced blood glucose, total cholesterol, triglycerides, HDL, LDL, and VLDL when fed with hesperidin 100mg/kg NW for 4 weeks [31]. Hesperidin was found in a study to exert antidiabetic effect by normalizing the expression ranges of insulin signaling and glucose metabolism related genes hexokinase - II, enolase – 1, and PI3 kinase p110δ that were previously disrupted in the liver of High fat diet – induced obese mice [32].

Hesperidin and hesperetin at 10μM inhibited the non-enzymatic glycation of proteins (65.57% and 35.6%, respectively), an important step in the production of advanced glycated end products (AGEs). The 2 flavonoids equally activated glucose uptake in L6 myotubes after short- and long-term treatment. The rate of 2-NBDG uptake by both compounds was comparable to that of Rosiglitazone, a conventional antidiabetic [30].

Hesperidin anticancer effects are linked to its antioxidant and anti – inflammatory effects, and its ability to reverse drug resistance in cancer cells. Hesperidin interacts with several cellular targets and pathways, and inhibits tumor proliferation by inducing apoptosis and cell cycle arrest [33]. In vitro treatment of prostate cancer cells with hesperidin resulted to significant reduction in cell proliferation in a dose-dependent manner. The reduction in cancer cells proliferation resulted from cell cycle arrest, and necrosis-like apoptotic cell death activated by intracellular accumulation of ROS molecules and decrease in mitochondrial membrane potential (MMP) [34]. Single treatment with hesperidin in a study, showed cytotoxicity against MCF – 7 cell lines resistant to doxorubicin (MCF- 7/Dox). Combined hesperidin and doxorubicin showed additive and antagonistic activities. Hesperidin did not increase apoptotic induction, but it reduced the P-glycoprotein (Pgp) expression level when combined with doxorubicin [35].

Naringenin: is a major citrus flavanone found in many fruits like grapefruits, sour orange, cherries, tomatoes. It is the aglycone metabolite of naringin which is found mainly in citrus fruits. Naringin a glycosidic flavanone is hydrolyzed in a 2-step reaction to naringenin, its aglycol structure by naringinase enzyme in the liver. Naringin does not have much nutrition importance apart from impacting the bitter taste and colored pigments to citrus fruits, while naringenin is colorless and tasteless.

Both flavanones exhibit wide range potent antioxidant, anti-inflammatory, nephroprotective, hepatoprotective, antidiabetic, anticancer, anti-apoptotic, immunomodulatory activities [36,37]. Naringin is less potent than naringenin owing to steric hinderance of the scavenging group by its sugar units.

Fibrosis, the final common pathology in most chronic illness is characterized by transdifferentiation of fibroblasts into myoblasts and excessive collection of extracellular matrix (ECM) produced by myofibroblasts. Naringenin is reported to prevent pathogenesis of fibrosis in vitro and in vivo through the regulation of several signaling pathways such as transforming growth factor-β1/small mother against decapentaplegic protein 3 (TGF-β1/Smad3), mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), sirtuin 1 (SIRT1), nuclear

factor-kappa B (NF – kB), or reactive oxygen species (ROS) [38]. Normoglycemic and Non-Insulin-Dependent diabetes mellitus (NIDDM) rat models were treated for acute and subchronic periods, with 50 mg/kg/day of naringenin intragastrically. Results showed significant reduction in plasma glucose in normoglycemic and NIDDM rat models ($p<0.05$) [39].

Naringenin administered to Gestational Diabetes Mellitus (GDM) mice improved GDM symptoms, glucose and insulin tolerance, inhibited inflammation, TNF-α-induced ROS production, enhanced GLUT 4 membrane translocation, and glucose uptake, that were neutralized by inhibition of AMP-activated protein kinase (AMPK) [40]. Naringenin (75μM, 2hr) treatment elevated glucose uptake L6 muscle cells. Naringenin also, significantly elevated 5' AMPK phosphorylation/activation and AMPK blockage using small interference RNA inhibited the naringenin-activated glucose uptake [36].

Naringin and naringenin anticancer effects are pleiotropic, regulating different cellular signaling pathways, inhibit cytokines and growth factor production and cause cell cycle arrest [41]. Naringin and naringenin exert their anticancer effects via various signal transduction pathways. Various studies have shown that naringin and naringenin have significant potent synergistic effects with conventional anticancer agents compared to monotherapy. Both, are known to overcome multidrug resistance in cancer cells [42].

Eriodictyol: is a hydroxylated flavonoid abundant in citrus, vegetables and medicinal plants.
Eriodictyol is reported to have widespread medicinal effects like antioxidant, anti-inflammatory, anticancer, antiobesity, antidiabetic, neuroprotective, cardioprotective, hepatoprotective etc [43].
Eriodictyol in a study was shown to increase insulin-activated glucose uptake in both human hepatocellular liver cancer cells (HepG2) and differentiated 3T3-L1 fat cells when administered high – glucose [44].

Eriodictyol equally up-regulated the mRNA expression of PPARy2 and adipocyte-specific fatty acid-binding protein (aP2) and also the protein concentration of PPARy2 in differentiated 3T3-L1 adipocytes. Eriodictyol also, reactivated Akt in HepG2 cells with high-glucose-induced insulin resistance, a response that was significantly blocked when pretreated with PI3K inhibitor LY294002 [44]. Diabetic retinopathy is a leading cause of blindness. Eriodictyol was found to offer protection against retinopathy on high glucose (HG) induced rat retinal ganglia cells (RGCs). It enhanced cell viability of HG-induced rat RGC-5 cells [45].

Eriodictyol decreased the reactive oxygen species production, and increased the effects of superoxide dismutase, glutathione peroxidase and catalase in rat RGC-5 cells in response to HG stimulation, and also decreases the formation of proinflammatory cytokines. This flavanone promoted the nuclear translocation of nuclear factor erythroid-2 (E2)-related factor 2 (Nrf2) and increased the expression of antioxidant enzyme heme-oxygenase-1 (HO-1) [45].

Retinoblastoma (RB) is one of the most common intraocular tumors in children. Eriodictyol inhibited the proliferation, migration, invasion and induced apoptosis of RB Y79 cell lines in a dose-dependent manner and reduced the expression of MMP-2 and MMP-9 proteins in the cells. It equally dose-dependently inhibited the activation ofPI3K/Akt signaling pathway. The induced apoptosis of RB was reversed by PI3K agonist 740 Y-P [46]. Eriodictyol showed the most potent inhibitory activity on cell viability of gastric cancer (GC) cells among the common flavonoids from Polygoni orientalis Fructus including quercetin, taxifolin, and kaempferol. This flavanone inhibited colony formation of GC cells and induced cell apoptosis, with PI3K/Akt signaling, the most common pathway among the anti-GC targets [47].

Eriodictyol exhibited IC50 value of 50μM against hman lung cancer cell line A549 and IC50 of 95μM against non-cancerous FR2 cells. It carried out its anticancer effect via induction of apoptosis by regulating the Bcl-2/Bax signaling pathway, and also dose-dependently inhibiting the mTOR/PI3K/Akt pathway. It mediated cell cycle arrest of A549 cells at G2/M phase and decreased mitochondrial membrane potential in a dose-dependent manner [48].

c)Flavans: flavans are widely found in nature and results from a double reduction of flavanones. They are lipophilic and are found mainly in the peel of unripe fruits and in cutin of leaf surfaces. Examples of flavans include Flavan-3-ols, flavan-4-ols and flavan-3,4-diols (leucoanthocyanidin).
Flavan-3-ols (Flavanols): are subgroup of flavonoids derived from flavans and commonly found in foods and beverages like tea, apples, blueberries, cherries, grapes, red wine and cocoa. Flavan-3-ols include catechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, proanthocyanidins, theaflavin, thearubigins.

Catechin: is a flavan-3-ol very important for its antioxidant role in plants and is a constituent of several medicinal plants and beverages.

Catechin and its stereo-isomers have reported anti-inflammation, antidiabetic, anticancer, antibacterial, neuroprotective, hepatoprotective, memory enhancing properties, majorly via its effect on NF-kB, Nrf-2, TLR4/NF-kB, COMT, and MAPKs pathways [49].

A new antidiabetic formulation was optimized from a mixture of catechin, epicatechin and rutin in a study on alloxan-induced Swiss diabetic mice, to obtain a new, safe, multitarget antidiabetic formulation for management of diabetes and its complications. The 3 molecules showed potent antihyperglycemic effect as single, binary and ternary combination against positive and normal control [50].

Catechin is the main bioactive antioxidant constituent of the green tea (Camellia sinensis) reputed for its anticancer and anti-inflammatory effects. Catechins showed significant ROS and nitrogen neutralizing effects. The class of green tea catechin

derivatives includes: epicatechin, epigallocatechin gallate, epicatechin gallate and epigallocatechin gallate. The last of these showed the most potent anticancer and anti-inflammatory effects [51]. Green tea catechins have been reported to effectively prevent lung, breast, esophageal, stomach, liver and prostate cancer [51]. The cancer chemopreventive roles of 10 classes of polyphenols viz caffeic acid, gallic acid, catechin, epicatechin, gallocatechin, catechin gallate, gallocatechin gallate, epicatechin gallate, epigallocatechin and epigallocatechin gallate, were studied; also, their structure-activity relationship on proliferation of HCT-116 and SW-480 human colorectal cancer cells. The result showed that the epigallocatechin gallate exhibited the most potent antiproliferative properties, and significantly induced cell cycle arrest in the G1 phase and cell apoptosis. The chemical structure activity relationship showed that the gallic acid group significantly promoted catechin's anticancer potential [52].

Proanthocyanidins (Condensed Tannins): are flavanols a subgroup of flavonoids. They are found in flowers, nuts, fruits, bark and seeds of various plants eg strawberry, cranberries, cinnamon, raspberry, wild blue berry, etc. where they impact them with various colours. Grape seed extract is one of the best-known sources of proanthocyanidins. The highest concentration of proanthocyanidins in fruit was found in black chokeberries.

Proanthocyanidins have multiple and varying medicinal properties which include antioxidant, anticancer, antidiabetic, neuroprotective and antimicrobial. Agricultural and food processing wastes contain great quantities of proanthocyanidins [53]. Proanthocyanidins also have multiple, and various pharmacological effects against free oxygen radicals (ROS). The concentration-dependent oxygen free radical scavenging properties of grape seed proanthocyanidin extract (GSPE), vitamin C and vitamin E succinate (VES) and also superoxide dismutase, catalase and mannitol against biochemically produced superoxide anion and hydroxyl radical were assessed in a study. At a 100mg/l concentration, GSPE showed 78 -81% inhibition of superoxide anion and hydroxyl radical. Under similar situation, vitamin C and VES inhibited superoxide anion by 12-19%, and 36-44% respectively [54].

At relatively low concentrations in the circulatory system, proanthocyanidins act as cell-signaling factors to regulate glucose homeostasis by modulating liver glucose production through adenosine monophosphate – activated protein kinase and/or insulin-signaling pathways. Higher proanthocyanidin intake is linked to decreased risk of diabetes. Proanthocyanidins also directly regulate pancreatic β-cell functions: inhibition of oxidative stress, promotion of insulin secretion and enhancement of β-cell survival [55]. In a study, 5 groups of 6 healthy rats each; group II and V were treated with single oral dose of proanthocyanidin (50mg/kg), group III received single dose of oral sitagliptin (40mg/kg) and group I and IV treated with vehicle serve as control. Oral or Intraperitoneal glucose were given after 30mins of treatments. Blood glucose was measured over 2 hr duration at (0, 30, 60, 90, and 120) min from glucose administration. Results showed that both proanthocyanidin and sitagliptin significantly enhanced hyperglycemia induced by oral glucose load compared to control [56].

A study was carried out to investigate for the first time, the genome-wide properties of oligomeric proanthocyanidins (OPCS) from grape seeds in colorectal cancer. Results of the study showed that OPCs affect some key cancer-linked genes. The genes associated with cell cycle and DNA replication were the most significantly and consistently affected by OPCs across many cell lines. OPCs more effectively inhibited the colorectal cancer cells than unfractionated grape seed extract [57]. A study investigated the effect of grape seed extract from Vitis vinifera (VGSE) on DNA and protein damage, labile iron properties and enzyme inhibitory activity. The study showed for the first time, that VGSE inhibit DNA and BSA damage, and labile iron activity in vitro. VGSE also inhibited in vitro effects of AChE, tyrosinase and α-amylase. VGSE significantly inhibited the viability of MCF-7, Hep-G2, Caco-2 and Huh-7 cells after 48-hr treatments [58].

d) Anthocyanins: these are water soluble colored flavonoid pigments very widely represented in plants. They are commonly referred to as nutraceuticals, with more than 600 of them found in natural food. Anthocyanins are the highest consumed flavonoids by man, but the least bioavailable of all flavonoids.

The pigments are glycosylated form (anthocyanin pigment derived by adding sugar molecules to anthocyanidins), and cyanidin-3-glucoside is the major anthocyanin found in plants. They are responsible for colors in plants, and used traditionally as natural food colorant. The color and stability of these pigments are affected by Ph, light, temperature and structure. They appear red in acid, violet in neutral, and blue in alkaline medium [59]. Dietary sources include red and purple berries, grapes, apples, plum, cabbage, or foods containing high levels of natural colorants. Cyanidin, delphinidin, malvidin, peonidin, petunidin, and pelargonidin are the 6 common anthocyanidins [60].

Anthocyanins exhibit wide range of pharmacological properties which include antioxidant, anti-inflammatory and anticancer [61].

The effect of purified anthocyanin on serum Insulin-like growth factor binding protein-4 (IGFBP-4) fragments and glycemic control in patients with elevated fasting plasma glucose was investigated in 121 patients with raised fasting glucose (≥5.6mmol/L) assigned to anthocyanins (320mg/day) or placebo groups. Results showed anthocyanins increased serum IGFBP-4 fragments and reduced fasting glucose compared with placebo [62]. Results of systemic reviews on the in vitro, in vivo and human studies of the antidiabetic effects of anthocyanins showed that these compounds inhibited various enzymes, and also regulated gene expression and metabolic pathways of glucose metabolism. Human clinical studies reported that high doses of anthocyanins showed significant effect in in prevention and treatment of type 2 diabetes [63].

The results of a systemic review, of selected studies from January 2000 to September 2021, on the anticancer properties of

anthocyanins carried out in vitro showed that anthocyanins have anticancer potentials by inhibiting cancer cell viability and proliferation, cell cycle modulation and enhancing apoptosis [64]. The phenolic structure of anthocyanins is responsible for their antioxidant effects. These effects have been reported in various cell cultures viz. colon, endothelial, liver, breast, leukemic cells, and in keratinocytes. In these cultures, anthocyanins showed wide range antitoxic and anticarcinogenic properties due mainly to their ability to scavenge ROS, chelating metals and by direct binding to proteins [65].

e) Flavones (flavus = yellow): are a subgroup of flavonoids which occur as yellow pigments in glycoside form and are used as dyes. They are common in foods, predominantly from spices, beverages and some yellow or orange fruits and vegetables. Examples of flavones include apigenin, luteolin, tangeretin, chrysin, wogonin, diosmin, baicalein.

Apigenin: is a polyphenol found mainly in plants – based foods like vegetables (parsley, celery, onions), fruits (oranges), herbs (chamomile, thyme, oregano, basil) and beverages (tea, beer, and wine). It exhibits potent antioxidant properties by scavenging free radicals, antidiabetic, anticancer, and neuroprotective properties [66,67].

Apigenin activates metabolism of glucose and transportation in the peripheral tissues. It promotes glucose metabolism through suppression of gluconeogenesis enzymes and aldose reductase, and hence prevent diabetic complications like cataracts, retinopathy and neuropathy that occurs when sorbitol diffuses out of cell membrane [68].

Apigenin (20mg/kg) treatment in Streptozotocin (STZ) – induced diabetic male albino Wistar rats with fasting blood glucose >250mg/dl, reduced renal dysfunction, oxidative stress, and fibrosis (reduced TGF-β1, fibronectin and type IV collagen), in the diabetic rats. It equally significantly inhibited MAPK activation, which inhibited inflammation (decreased TNF-α, IL-6, and NF-kB expression) [69].

Apigenin enhances apoptosis by activating extrinsic caspase – dependent pathway by upregulating the mRNA expressions of caspase – 3, downregulation of NF-kB p105/p50, PI3K, Akt expression, and phosphorylation of p-Akt [70].

A systematic review and meta-analysis of 25 studies on anticancer properties of Apigenin on different cancer types like liver, prostate, pancreatic, lung, nasopharyngeal, skin, colon, colorectal, head and neck squamous cell carcinoma, leukemia, renal cell carcinoma and breast cancer. Result showed that apigenin reduces tumor volume, tumor weight, tumor number and tumor load [71]. Apigenin carries out anti-tumor activities by inducing apoptosis/cell-cycle arrest [71].

Luteolin: is a flavone which occur naturally in its glycosylated form and is found to be present in high amount in peppers and chilis, and also found in lemons, watermelon, navel oranges and red grapefruit.

Antidiabetic effect of luteolin (LU) and luteolin-7-O-glucoside (LUG) were studied on KK-Ay mice. The investigation showed that both LU and LUG significantly enhanced blood glucose, HbA1C, insulin, and HOMR-IR levels, with LU more potent than LUG. Also significantly reduced were TGs and mRNA expression of fatty acid expression – related genes (SREBP-1C) [72]. The antidiabetic effect of luteolin (LUT) on streptozotocin (STZ, 50mg/kg b.w) - induced diabetic rats was investigated and showed that oral LUT supplementation for 21 days resulted significant reduction in blood glucose, oxidative stress, proinflammatory cytokine levels, and modulated hyperlipidemia profile [73].

Luteolin has various biological activities like anti-inflammation, antiallergy, anticancer etc. and equally has antioxidant and pro-oxidant biochemical effects [74]. Luteolin exhibit anticancer effects through downregulation of key regulatory pathways linked with oncogenesis and oxidative stress; it induces cell cycle arrest, upregulation of apoptotic genes, and inhibition of cell proliferation and angiogenesis [75].

A review of the anticancer effect of luteolin reported it to possess anticancer effects against lung, breast, glioblastoma, prostate, colon, and pancreatic cancers. It inhibits cancer development in vitro and in vivo and in addition reverses epithelial – mesenchymal transition (EMT) via cytoskeleton shrinkage, activation of epithelial biomarker E-cadherin expression, and by down-regulation of the mesenchymal biomarkers N-cadherin, snail, and vimentin [76].

f) Isoflavones: These are specific type of isoflavonoids, and a class of phytoestrogens that have both estrogen and antiestrogen effects; and find use in ameliorating menopause symptoms or preventing osteoporosis in postmenopausal women. They are equally blamed for rising breast cancer and prostate cancer risks in women and men respectively. Isoflavones occur almost exclusively in the bean family, for example soyabeans, that mimic the action of estrogen hormone.

Genistein, daidzein and glycitein are the most bioactive isoflavones found in soy beans. Phytoestrogens have similar structures to human female sex hormone 17-β-estradiol, which can bind both α and β estrogen receptors, and mimic the action of estrogens on target organs, hence demonstrating several pharmacological properties when used in hormone dependent diseases [77]. Isoflavones are chemotherapeutic and find use as alternative therapy in several hormonal dependent cancers and diseases like breast, prostate cancers, cardiovascular and metabolic diseases [77,78]. They equally possess antioxidant, anti-inflammatory, antiangiogenetic, hepatoprotective, antidiabetic, antilipidemic and neuroprotective properties [79].

The pharmacological potencies and efficacies of isoflavones depends on their biological activity and bioavailability. Glucose-conjugated isoflavones are polar and water-soluble and have weaker biological effects than the aglycone isoflavones [77].

Epidemiological, preclinical (in vitro and in vivo) and clinical studies reported Isoflavones to be effective in the prevention and treatment of diabetes [80]. The relationship between regular intake of soyfoods and major isoflavones and risk of type 2 diabetes in Vietnamese adults was studied. The result showed that higher intake of total soyfoods was significantly linked with an inverse risk of type 2 diabetes; a lower risk was also reported for higher total isoflavone intake [81]. In a study to demonstrate the effect of Isoflavones on lipid and glucose metabolism, male and female Zuker rats (OZR) were used as models of type 2 diabetes. OZR fed on high isoflavone soy protein diet showed enhanced lipid metabolism similar to the observation in human treated with antidiabetic PPAR agonists such as fibrates and glitazones. Isoflavone-containing soy extract was equally reported to double PPAR-directed gene expression ($p<0.05$) in RAW 264.7 cells containing either a PPARalpha or PPARgamma expression plasmid [82].

Many epidemiological studies have investigated the association between soy consumption and breast cancer, with conclusion that dietary soy consumption lower the risk of breast cancer. There are several conflicting explanations on the actual anticancer mechanism of isoflavone. It appears that soy isoflavones act as weak estrogen, and equally demonstrates potent anti-estrogen effects. Thereby, modulating breast cancer risk by synergizing or antagonizing the estrogen receptor (ER) and ER-independent signaling pathways [83,84].

A systematic review of the literature to find out if the quantity of isoflavones consumed has positive effect in pre- and post-menopausal women was carried out. Results from analysis of data from prospective studies, showed a clear inverse significant association between the quantity of isoflavones consumed and breast cancer occurrence in pre- and post-menopausal women [85]. Idronoxil, is a first generation synthetic isoflavone anticancer agent. It is a regulator of many signal transduction pathways, exerting wide range of pharmaceutical effects, like cell cycle arrest, apoptosis, immunomodulatory and antiangiogenesis; with potentials to synergize and complement wide range of chemotherapeutics [86].

2. Phenolic Acids: These are polyphenols that occur naturally in plants. They make up about 30% of all polyphenols and are found in fruits (berries), vegetables, cereals, seeds and beverages. Phenolic acids are made up of benzoic acid derivatives, like p-hydroxybenzoic acid, salicylic acid, vanillic acid, syringic acid, gallic acid, ellagic acid, and Cinnamic acid derivatives, like p-coumaric acid, caffeic acid, sinapic acids and ferulic acid.

Phenolic acids, has phenol moiety and resonance stable structure that can donate H-atom leading to antioxidant effect via free radical scavenging. Other radical scavenging mechanisms by phenolic acids include: radical quenching through electron donation and singlet oxygen quenching. Phenolic acids also have reported antimicrobial, anticancer, antimutagenic, anti-inflammatory etc properties [87].

Phenolic acids are reported to increase glucose uptake and glycogen synthesis, and enhance glucose and lipid profiles in obesity and diabetes mellitus [88].

The bioassay of phenolic acid (PA) rich fractions from methanolic extracts of Aerva lanata L. (F. amaranthaceae), revealed high DPPH and ABTS+ scavenging activity, with high antiradical, and strong xanthine oxidase and lipoxygenase inhibitory effects. The fractions equally showed α-amylase and α-glucosidase inhibitory effects. The bioactivities of fractions strongly correlated with the presence and total PA content [89].

Phenolic acids and their derivatives have reported anticancer effects in various human cancer cell lines viz. breast, cervical, adenocarcinomas, and leukemias. The trihydroxylated derivatives showed better effects than dehydroxylated ones [90]. Renin-angiotensin system (RAS) are involved in cancer progression vis angiotensin converting enzyme (ACE), by activating and upregulating many oncogenic factors. Phenolic acids and their derivatives (ellagic acid, gallic acid, caffeic acid) have reported inhibition of ACE, with consequent chemopreventive and chemotherapeutic activities [91]. Acetylsalicylic acid (ASA) and salicylic acid (SA) exhibited anticancer activities against the murine model of grafted melanoma and also, cultured melanoma B16F10 cells. The drugs enhanced pro-apoptotic activities in both in vivo and in vitro models, by activating endoplasmic reticulum stress which results in the upregulation of the pro-apoptic transcription factor C/EBP homologous protein (CHOP) [92].

3. Lignans: these are polyphenolic bioactive compounds found in fruits, vegetables, whole grains, legumes and seeds of plants. Important sources include cruciferous vegetables, flaxseeds, sesame, berries, pumpkins, brussel sprouts.
Lignans are classified into eight structural subgroups according to the way oxygen is incorporated and patter of cyclization viz. furan, furofuran (pinoresinol), dibenzylbutane (secoisolariciresinol), dibenzylbutyrolactone (matairesinol), aryltetralin (podophyllotoxin), arylnaphthalene (justicidin A), dibenzocyclooctadiene (steganacin) and dibenzylbytyrolactol [93].

Majority of plant lignans in human food are biotransformed by the intestinal microflora in upper part of large intestines to enterolactone and enterodiol, known as mammalian or enteroligans [94]. Although, most studies on phytoestrogen – rich foods focused on soy isoflavones, lignans are the major source of phytoestrogens in typical western diet [95,96]. Lignans are bioactive compounds with reported wide range activities including anti-inflammatory, antioxidant and anticancer effects [93]. Lignans have very high content of antioxidants.

Furofuran ligands like samin, sesamin and sesamolin have reported antidiabetic properties with preventive and curative effects. The exhibit inhibitory effects against α-glucosidase and free radicals, with lignans having free hydroxyl group having more potent effects [97]. 22 products of furofuran lignans were investigated against 3 different α-glucosidases (maltase, sucrase and baker's yeast glucosidase) and DPPH radical. β-14 with 2 catechol moieties and 1 acetoxy group, was the most potent inhibitor of the α-glucosidases, of all the furofuran lignans studied

[98]. β-14 inhibitory effect against Barker's yeast was 28 times more than the standard drug acarbose, and its DPPH radical scavenging was 130 times more than the commercial antioxidant BHT [98]. A systematic review of scientific literatures on the beneficial effects of Magnolol, a lignan from Magnolia bark, on type 2 diabetes parameters like glycemia, lipid metabolism, and oxidative stress was carried out. Results showed that lignan is a promising agent and can be used as adjunct to conventional antidiabetics [99].

Lignans have potent chemotherapeutic and chemopreventive effects among the phenolic compounds, in addition to other medicinal properties like antioxidant, anticarcinogenic, antimutagenic, and anti-estrogenic effects [100].

Various researches reported that the most remarkable bioactive effects of lignans are their anticancer effects. A review of studies on the anticancer properties of lignans, including their sources, active plant parts, extracts and various cell lines used on, concluded that lignans to be effective chemotherapeutic agents in near future [101]. The therapeutic effects of purified flaxseed hydroxylate (PFH) which is a lignan rich fraction, on human breast cancer cell lines (T47D and MCF-7) and mice bearing tumor was investigated. Results showed cytotoxicity against the cell lines, with the reduction of expression of metastasis marker, 1-α, metalloproteinases, and VEGF, an important activator of angiogenesis; and increased caspase-3-dependent apoptosis [102]. Equally reported was the effect of dietary intake of flaxseeds, fixed oil or flax meal on mice-bearing solid Ehrlich ascites carcinoma for 3 weeks; resulting in decrease tumor volume, expression of estrogen, insulin growth factor, progesterone, VEGF and MMP-2, and increased expression of caspase - 3 [102].

4. Stilbenes: these are phytoalexins polyphenols found mainly in grapes (skin), red wine, peanuts and berries in mostly glycosylated cis and trans isomeric forms. Examples include resveratrol, piceatannol, pterostilbenes.

Stilbenes are biosynthesized as a result of biotic and abiotic stresses such as microbial infections, high temperatures, and oxidation [103]. Researches have reported stilbenes to exhibit multiple pharmacological properties like antioxidant, antimicrobial, anti-inflammatory, anticancer, antiobesity, antidiabetic, antiaging, neuroprotective, cardioprotective effects [103,104].

Several numbers of in vivo researches showed resveratrol (RES) to possess glucose – lowering activity in type 1 and 2 Diabetes mellitus, through improving insulin sensitivity and preservation of pancreatic beta – cells [105,106].

A Systematic review and meta-analysis of studies on the effects of resveratrol on glucose control and insulin sensitivity in type 2 diabetes was carried out. Results showed that resveratrol significantly improved fasting plasma glucose ($p<0.01$) and insulin levels ($p<0.0001$). The drug equally decreased HOMA – IR index, systolic blood pressure and diastolic blood pressure [107]. Pterostilbene (PTE) is a natural demethylated analog of resveratrol, with antioxidative, hypolipidemic and hypoglycemic properties. STZ, high-sugar and high-fat diet induced diabetic rats were treated with PTE (20, 40, and 80 mg/kg/d) for 8 weeks. Results showed PTE significantly decreased weight loss, FBG, Insulin resistance, serum lipid levels and inflammatory factors. PTE also inhibited oxidative stress, by reducing MDA expression and increasing SOD expression [108].

Resveratrol has both chemotherapeutic and chemopreventive roles against many human cancers like breast, cervical, uterine, ovarian, kidney, liver, bladder, thyroid, prostate, esophageal, stomach, colon, head and neck [109]. Studies have shown that resveratrol reverses multidrug resistance in cancer cells, and synergizes with conventional chemotherapeutics. Several novel analogues of resveratrol have been developed with improved anticancer, bioavailability and pharmacokinetic profiles [110].

B) Terpenes: They are highly aromatic compounds that confers scent on many plants.
Terpenoids (Isoprenoids): are the largest (60% of natural products) and most diverse group of compounds produced by plants and are modified terpenes with different functional groups and oxidized methyl groups. Terpenoids derivatives depending on the number of isoprene (carbon) units are called, hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes, tetraterpenes polyterpenes etc. Examples are farnesene, taxadiene, lycopene, astaxanthin.

Other classes of terpenoids include: steroids, taxanes, tocopherols, artemisinins, cannabinoids and ingenanes. Examples of drugs derived from biologically produced terpinoids are artemisinin (sesquiterpenoid), vincristine (meroterpenoid), taxol (diterpenoid), cortistatin. Triterpinoids presnt in M. charantia and Elephantopus scaber (elephant foot plant) possesses antidiabetic effects [111].

Terpinoids have potent and diverse antioxidant effects. Monoterpenes and diterpenes or essential oil have reported antioxidant effects in vitro. The newly discovered gamma-terpenes are equally very effective antioxidants [112]. Terpinoids antioxidant activities contribute to the health promoting effects of fruits and vegetables. The 3 main antioxidant effects of carotenoids are via quenching of singlet oxygen, hydrogen transfer or electron transfer. The monoterpenes limonene and perillyl alcohol are promising chemotherapeutics. Combination of hydrophilic and hydrophobic antioxidants exert synergistic properties as seen in rutin combination with gamma-terpinene, lutein or lycopene [112].

1. Monoterpenes: are dimers of isoprene, made up of only carbon and hydrogen atoms, with C10 H16 structure and are divided into acyclic, monocyclic, bicyclic, and tricyclic compounds. Monoterpenoids are modified monoterpenes containing oxygen and nitrogen atoms, with distinct functional groups like phenols, ketones, aldehydes, carboxylic groups and alcohols.

Monoterpenes are present in essential oils extracted from various fruits, vegetables, spices and herbs. Examples of monoterpenes and monoterpenoids include α-pinene, β-pinene, terpin-

eol, camphor, menthol, limonene, carvone, geraniol, linalool, nerol, cetrol.

D-limonene, a monocyclic monoterpene found in large quantities in citrus fruits like lemon, orange and grape has reported potent antioxidant, antidiabetic, anticancer, anti-inflammatory, cardioprotective, gastroprotective, hepatoprotective, immunomodulatory, antifibrotic and anti-genotoxic properties [113].

Review of in vitro and in vivo researches published in scientific literatures showed that both the aglycone and glycosides compounds of, small structural sized, monoterpenes exhibited antidiabetic, antiobese and lipid reducing properties [114]. Important pharmacological targets include insulin signaling pathways and/or the associated PI3K-AKT (protein kinase B), peroxisome proliferator activated receptor-y (PPARy), glucose transporter -4 (GLUT4) and adenosine monophosphate-activated protein kinase (AMPK) pathways; proinflammatory cytokines and the NF – kB Pathway; glycogenolysis and gluconeogenesis in the liver; glucagon-like-1 receptor (GLP-1R) [114]. STZ (40mg/kg b.w) intraperitoneal-induced diabetic rats in a study, received citronellol, a citrus monoterpene orally at doses 25, 50, and 100 mg/kg b.w for 30 days. Results showed dose dependent improved insulin, Hb, and hepatic glycogen with significant reduction in glucose and HbA1C levels. The altered effects of carbohydrate metabolic enzymes, hepatic and kidney markers were restored to near normal. Citronellol supplement equally preserved the structures of hepatic cells and insulin-positive β-cells in STZ-rats [115].

A systematic review of anticancer activities of monoterpenes in 39 articles published from 2015 to 2019 showed that monoterpenes have cytotoxic effects in a wide variety of tumor cell line, and exert this property majorly by induction of apoptosis as a result of oxidative stress [116].

Another review of the anticancer effects of monoterpenes found in essential oil was carried out. Results showed that carvacrol and linalool were the most researched monoterpenes, and were highly significant effective inhibitors of various tumors in vitro and in vivo. Apoptosis was their major mechanism of actions, followed by cell cycle impairment, ROS production, autophagy, necroptosis, etc. [117]. D-Limonene and its derivatives showed reported chemopreventive and chemotherapeutic effects in preclinical and clinical studies. A scoping and critical review of records on the effect of d-limonene or its derivatives on breast cancer in humans was carried out. Results showed d-limonene to be safe and tolerable in subjects compared to its derivative, perillyl alcohol. Also reported was dearth of clinical studies in this regard [118].

2. Diterpenes: these are terpinoids found mainly in coffee beans and have molecular formular C20 H32. They form the basis for important biological compounds like retinol, retinal, and phytol. The coffee oil is rich in diterpenes especially cafestol and kahweol, which are mainly present in the esterified form with different fatty acids. Despite their beneficial properties of anti-angiogenic and anti-carcinogenic activities, diterpenes are equally linked to elevation of blood cholesterol [119], triacylglycerols, LDL and liver enzymes. Studies have shown that a cup unfiltered coffee contains 30 times more diterpenes than a cup of filtered coffee.

A comprehensive critical review of literatures on the potentials of diterpenes as antidiabetic agents published from 1995 to September, 2021, reported 427 diterpenes to have different degrees of antidiabetic properties. Steviol glycosides, stevioside and rebaudioside A, were the most investigated diterpenes with potential antidiabetic effects using in vitro and in vivo models, as well as human subjects. Stevioside and rebaudioside A, are the only diterpenes that progressed to the clinical trial stage of drug discovery [120].

Inhibition of α-glucosidases and protein tyrosine phosphatase 1B (PTB 1B), and PPAR-y agonist effects were the most frequent used models for studies. The molecular mechanism of actions of diterpenes include increased GLUT4 translocation, and activation of PI3K and AMPK dependent signaling pathways [120].

Diterpenes can be classified as linear, bicyclic, tricyclic, tetracyclic, pentacyclic and macrocyclic compounds based on skeletal core. A comprehensive review of natural diterpenes with abietane, clerodane and labdane skeleton revealed various degrees of cytotoxicity and anticancer properties against different cancer cell lines [121]. Acyclic diterpenes extracts from Irish Brown Seaweed Bifurcaria bifurcate were tested against human breast cancer cell line (MDA-MB-231). Results showed that several compounds of these extracts moderately inhibited the growth of the MDA-MB-231 cell lines [122].

3. Triterpenes: this is a very broad class of terpenes with wide structural diversity and broad range of biological activity. They have 3 terpene units (C10 H16), and 6 isoprene units, with molecular formular of C30 H48. There are about 20, 000 triterpenes found in nature, in animals, plants and microorganisms. Their most common structures are pentacyclic triterpenes, examples oleanane, ursane, taraxerane, taraxastane, lupane; tetracyclic triterpenes, examples dammarane and cucurbitane. Triterpenoids are triterpenes with heteroatoms, usually oxygen and examples include ursolic acid, oleanolic acid, betulinic acid, celastrol, pristimerin, lupeol and avicins.

Several studies reported triterpenes to exhibit potent antidiabetic effects. They inhibit enzymes linked to glucose metabolism, exhibit hypolipidemic and antiobesity effects, enhance insulin sensitivity and normalize plasma glucose and insulin levels. They have powerful antioxidant effects and inhibit the formation of advanced glycation end products, involved in the pathogenesis of diabetic nephropathy, embryopathy, neuropathy or impaired wound healing [123].

Triterpenes showed promising potentials in the treatment of diabetic retinopathy, neuropathy and nephropathy, or in impaired wound healing by inhibiting various pathways involved in diabetes and its complications [124]. Oleanolic acid (OA) enhance insulin response, preserves functionality and survival of β-cells

and protects against diabetes complications. OA directly regulates enzymes linked to insulin biosynthesis, secretion and signaling. It interacts with the transduction pathways and activates transcription factor Nrf2; and so, induces the expression of antioxidant enzymes and phase II response genes, inhibits NF-kB, and blocks the polyol pathway, AGEs production and hyperlipidemia [125].

Triterpenes viz. oleanane, ursane, and cucurbitacins have reported anticancer, anti-inflammatory, antiproliferative and pro-apoptotic effects. Review of several preclinical (in vitro and in vivo) studies showed that terpenoids have chemotherapeutic and chemopreventive effects on animal models of colon, breast, prostate and melanoma cancer [126]. In signaling network, triterpenes primarily target membrane receptors which controls and regulates expression level of the biological responses. Triterpenes target nuclear factor kappa B, toll – like receptors, signal transducer and activator of transcription 3, and PI3K/Akt/mTOR [127]. Triterpenoids are characterized by basic backbone modified in various ways, permitting the formation of more than 20, 000 naturally occurring triterpenoid varieties. Various triterpenoids, including ursolic and oleanolic acid, betulinic acid, celastrol, pristimerin, lupeol, and avicins possess anticancer, and anti-inflammatory activities. To enhance these anticancer effects, synthetic triterpenoids derivatives have been produced. These include cyano-3,12-dioxooleana-1,9 (11)-diene-28-oic (CDDO), its methyl ester (CDDO-Me) derivative, both of which are under phase I studies investigation with betulinic acid [128].

Saponins: Saponins are a subgroup of terpenoids known as triterpene glycoside. Saponins are made up of a triterpene aglycone connected to one, two or three saccharide chains, making them very amphipathic. The amphipathic nature gives saponin surfactant effect and ability to interact with cell membrane constituents like cholesterol and phospholipids, and also important for making soaps and cosmetics.

The antioxidant effect of saponin was investigated in a study by DPPH and nitric oxide free radical scavenging effects, while the antidiabetic properties were evaluated by α- amylase and α- glucosidase inhibitory effects of saponin extract. Results revealed that saponin extract, compared with quercetin, showed better DPPH and NO radical scavenging activities. Also, saponin extract elicited stronger α- glucosidase and moderate α- amylase inhibitory effects compared to acarbose [129].

Insulin release was enhanced by administration of saponin, isolated from M. cymbalaria, in rat insulinoma cell line (RIN-5F) preexposed to adrenaline (5 µM) and nifedipine (50µM). Pancreatic histology equally showed significant quantitative increase in beta cells (75%) when treated with the saponin [130].

Saponins are found in more than 100 families of plants, out of which 150 types of natural saponins have reported significant anticancer activities. There are 11classes of saponins including dammaranes, tirucallanes, lupanes, hopanes, oleananes, taraxasteranes, ursanes, cycloartanes, lanostanes, cucurbitanes and steroids. Ginsenosides, belonging to dammaranes, inhibits tumor angiogenesis and metastasis. Dioscin, of steroidal saponin, and its aglycone diosgenin causes cell cycle arrest and apoptosis. Oleanane saponins with anticancer properties include avicins, platycodons, saikosaponins, soysaponins and tubeimosides (a natural analogue of oleanane saponins) [131].

Despite the many investigations and studies that reported significant anticancer properties of saponins, there are no known FDA-approved saponin – based anticancer drugs. This is due to several limitations like toxicities and drug - likeness effects. Newer studies are investigating the feasibility of combination therapy and drug delivery systems to increase bioavailability, efficacy and decrease toxicity in saponin [132].

4. Tetraterpenes: these are terpenes made up of 8 isoprene units with molecular formula of C40 H64. **Carotenoids**, which are large family (more than 600) of red, yellow, orange naturally occurring pigments used by plants for growth, color and photosynthesis, are widely occurring tetraterpenoids. They are divided into xanthophylls or oxycarotenoids (hydroxy-, oxy-, epoxy- and furanoxy groups) like lutein, canthaxanthin and astaxanthin, and carotenes (hydrocarbon carotenoids) like lycopene, α-carotene, and β-carotene; and are found in fruits, vegetables, fungi, and flowers.

Some carotenoids like β-carotene and β-cryptoxanthin are referred to as provitamin A carotenoids. The non-provitamin A carotenoids, are important in prevention of chronic diseases like CVD, age – related macular degeneration, and cancer [133]. Lutein and zeaxanthin have reported beneficial properties in eye health, via blue-light filtering and antioxidant effects. Astaxanthin antioxidant effect correlates its CVD and atherosclerosis prevention. The antiobesity effect of the brown sea weed carotenoid, fucoxanthin, is linked to induction of UCP 1 in abdominal white adipose tissue (WAT) mitochondrial, resulting in fatty acid oxidation and heat production in WAT [133].

A review of journals on the antidiabetic and antioxidant effects of carotenoids showed that Beta-carotene is the most widely occurring carotenoid in food, it has chemopreventive and insulin releasing effects. Both beta-carotene and lutein antioxidant effects play roles in preventing macular degeneration. Lutein has anticancer properties and decreases the ROS levels in the retina of diabetes. Lycopene protects diabetes patients from CVD. Astaxanthin showed potent hypoglycemic activities [134].

Carotenoids, like astaxanthin, zeaxanthin, bixin, beta-carotene, lutein, lycopene all have reported significant antidiabetic effects. Various studies have established the inverse association between body carotenoid level and risk of developing diabetes mellitus [135]. Carotenoids equally have reported role in the treatment of diabetes through promoting insulin sensitivity. They also, protect the body from the various chronic effects of diabetes like infectious diseases, nephropathy, neuronal and eye complications [136].

A review of literature on the association between the 6 most most common carotenoids in diet and 10 of the most commonly

diagnosed cancers was carried out using preclinical, epidemiological and toxicology data. Results revealed that several carotenoids showed beneficial effects in inhibiting carcinogenesis [137]. Various preclinical researches showed that carotenoid exhibited their anticancer effects through targeting multiple molecular events. They act by inhibiting cell proliferation and inducing apoptosis. Several carotenoids including lycopene, crocin, β-carotenoid, lutein, zeaxanthin, β-cryptoxanthin, astaxanthin, and fucoxanthin has significant anticancer effects through modulation of different cell signaling pathways [138].

C) Organosulfur Compounds: are compounds containing at least one carbon – sulfur bond. Organosulfur rich plants include allium (garlic, onion, chive, leek), cruciferous vegetables, other vegetables (like spinach, tomatoes, carrots, potatoes, mustards), fruits (avocardo, watermelon, pineapple) and cereals.

1. Thiols: Also known as mercaptans, are organosulfur compounds of R-SH, found in nature in complex combinations. They are analogous to alcohols, except that the suffix -thiol replaces -ol. The sulfhydryl or thiol (-SH) group made up sulfur and hydrogen atom attached to a carbon atom differentiate thiols from compounds like phenol and alcohol with oxygen - carbon bond structure. Examples of thiols are methanethiol, ethanethiol, 1-propanethiol, 2-propanethiol, 2-propenethiol (allyl mercaptan), butanethiol. Circulating thiol concentration shows the redox the redox status of the body systems, because free thiols are oxidized by ROS.

The thiol redox status of intracellular and extracellular compartments is important in the regulation of enzymes and transcription factors activities. Thiol antioxidant function via several mechanisms like, as part of the thiol/disulfide redox buffer, as metal chelators, as radical quenchers, as substrates for specific redox reactions (GSH), and as specific reductants of individual protein disulfate bonds (thioredoxin) [139]. Cells have produced other ways of elevating intracellular concentrations of thiols like GSH and thioredoxin in response to different kinds of stress. Exogenous thiols have equally been used to increase cellular and tissue thiols in preclinical and clinical studies. Various types of thiol-related compounds are used for these reasons like GSH and its derivatives, cysteine and NAC, dithiols like lipoic acid, which is reduced to the thiol form intracellularly, and "prothiol" compounds like OTC, that are enzymatically converted to free thiols intracellularly [139]. Examples of thiol drugs include N-acetylcysteine, 2,3-meso-dimercaptosuccinic acid, British anti-Lewisite, D-penicillamine, amifostine, etc [140].

In a case-controlled study to show that there is a reduced synthesis and irreversible utilization of glutathione (GSH) in type 2 (T2DM) diabetes particularly in the presence of microvascular complications, 16 patients with T2DM and 8 age- and sex-matched non-diabetic controls were recruited. GSH synthesis rate was measured using infusion of (2H2)- glycine as isotropic tracer. Results showed that compared to controls, T2DM patients had lower erythrocyte GSH level and absolute synthesis rates, but not fractional synthesis rates. The order of changes in patients with complications were greater for both GSH concentration and absolute synthesis rates ($p \leq 0.01$), compared to controls [141]. A novel series of multifunctional benzimidazole thiols were shown to be potent inhibitors of α-glucosidase. Results of bioactivity assessment showed that all of the compounds are potent inhibitors of this enzyme compared to acarbose [142].

Glutathione (GSH) is the most abundant thiol and antioxidant in living tissues and has many roles especially in maintenance of cellular redox homeostasis. It has both beneficial and pathogenic functions in many different malignancies. It is important in the detoxification and elimination of carcinogens [143]. GSH deficiency, or decreased GSH/glutathione disulphide (GSSG) ratio, leads to an increased susceptibility to oxidative stress involved in tumor progression. Excess GSH levels has dual opposing effects: 1. It increases the antioxidant property and resistance to oxidative stress seen in many cancer cells; 2. It enhances tumor progression, and increased levels correlates with metastasis [143,144]. Targeting GSH synthesis/utilization is a potential way of rendering tumor cells more susceptible to various chemotherapeutic and radiotherapeutic treatment modalities [143].

2. Glucosinolates: these are large groups of sulfur-containing glucosides found in cruciferous vegetables. Glucosinolates are thioethers made up of b-D-thioglucose, linked by an ester bond to an organic aglycone; which upon hydrolysis during food preparation, chewing, and digestion, are broken down, by plants or bacteria myrosinase (β-thioglucosidases), into bioactive constituents like indoles, nitriles, thiocyanates and isothiocyanates. Glucosinolates are grouped into 3 classes depending on the structure of their amino acid precursors: aliphatic glucosinolates (glucoraphanin), indole glucosinolates (glucobrassicin), and aromatic glucosinolates (gluconasturtiin).

Dietary Glucosinolates and flavonoids demonstrate anticancer properties by inhibiting the production of endogenous and exogenous carcinogens, thereby preventing the initiating of carcinogenesis. Glucosinolates act by activating antioxidant and detoxifying enzymes like glutathione-S-transferase and UDP-glucuronosyl transferase, and by inhibition of carcinogen-activating enzymes like cytochrome P450 1A1. Flavonoids and other phenolic antioxidants act by direct free-radical scavenging [145].

a) Isothiocyanates: these are the –N=C=S, functional groups produced by substituting the oxygen in the isocyanate groups with sulfur.

Isothiocyanates are biologically active hydrolysis products of glucosinolates. Cruciferous vegetables contain different types of glucosinolates, that form the isothiocyanates when broken down. For instance, broccoli is a source of glucoraphanin (the glucosinolate precursor of sulforaphane), and singrin (the glucosinolate precursor of allyl isothiocyanate). Watercress is a rich source of gluconasturtiin (the precursor of phenethyl isothiocyanate), and garden cress is rich in glucotropaeolin (the precursor of benzyl isothiocyanate) [146].

Sulforaphane (SFN) has reported effectiveness against metabolic diseases with antiobesity, antidiabetic and antioxidative effects. The administration of various doses of SFN increased serum insulin level, enhance HOMA-β index, reduced fasting

blood glucose, total cholesterol, LDL-C, and FGF 21 levels. SFN equally increased liver antioxidant abilities. High (10mg/kg) dose of SFN significantly reduced serum lipopolysaccharide levels [147]. SFN decreased body weight, fasting blood glucose and hyperlipidemia in high fat diet-fed mice. SFN potently increased glucose uptake and enhanced insulin signaling in palmitic acid-induced HepG2 cells. SFN equally increased expression of antioxidant genes downstream of Nrf2 and decreased accumulation of lipid peroxides MDA and 4-HNE, both in vivo and in vitro. SFN significantly decreased glutathione peroxidase 4 inactivation-mediated oxidative stress by activating the AMPK and Nrf2 signaling pathways [148,149].

Isothiocyanates are conjugated with glutathione in plants and animals, to produce dithiocarbamate, that is further metabolized to mercapturic acid, which is excreted in urine. Epidemiological researches have shown inverse correlation between cancer risks and isothiocyanate intake or excretion, especially with lung cancer. These researches were equally consistent in reporting a gene-environmental interaction, with a more effective protection in people null for the GSTM1 or GSTT1 genotype [150].

Sulforaphane is the most extensively researched isothiocyanate, based on its anticancer properties. It has been found to inhibit various human cancer cells like pancreatic, hepatocellular, and ovarian [151].

It equally inhibits breast, prostate, colon, skin, lung, gastric or bladder cancers. Sulforaphane has opposing health effects: 1. It acts as an antioxidant by activating the Nrf2-Keap 1 signaling pathway, thus promoting the effects of phase II detoxifying enzymes and trapping free radicals. 2. SFN increases intracellular ROS levels and reduces GSH, resulting in inhibition of T cell activation and T effector functions, thereby interfering with successful administration of immunotherapy by immune checkpoint inhibitors or CAR T cells [152]. SFN exhibits anticancer activities by modulating key signaling pathways and genes involved in the induction of apoptosis, cell cycle arrest, and inhibition of angiogenesis. SFN equally upregulates a series of cytoprotective genes by activating nuclear factor erythroid-2-(NF-E2-) related factor 2 (Nrf2), a critical transcription factor activated in response to oxidative stress; Nrf2 activation equally play a role in the cancer-preventive activities of SFN [153]. Epigenic alterations contribute to inhibition of tumor suppressor genes and activation of oncogenes. Studies on SFN anticancer effects reported that SFN can reverse epigenetic alterations in cancers by targeting DNA methyltransferases (DNMTs), histone deacetyltransferases (HDACs) and noncoding RNAs [153]. SFN has equally been reported to potentiate the activity of several classes of anticancer agents like paclitaxel, docetaxel and gemcitabine via additive and synergistic effects [154].

b) Indoles: are crystalline, aromatic, heterocyclic, organic, alkaloid molecules with C8 H7 formula. Indoles occur widely in nature and are produced by decomposition of proteins containing tryptophan by different bacteria. The indole test is a biochemical test on bacteria to determine its ability to convert tryptophan into indole.

Indoles, including indoles-3-carbinol (I3C) and its derivatives, are the products of the glucosinolate, glucobrassicin (present in cruciferous vegetables), hydrolysis catalyzed by the enzyme myrosinase [155]. 13C and its dimer DIM have reported pleiotropic protective effects on chronic liver injuries, viz. viral hepatitis, hepatic steatosis, hepatic cirrhosis, hepatocellular carcinoma. Indoles, regulate transcriptional factors and their signaling pathways, reduce oxidative stress and inhibit DNA synthesis to modulate the activation, proliferation and apoptosis of target cells [155]. Among the indole classes, 2-arylindoles are very promising in the lead for drug development. The derivatives of 2-arylindoles have reported antibacterial, anticancer, antioxidant, anti-inflammatory, antidiabetic, antiviral, antiproliferative, antituberculosis properties [156].

A review of antidiabetic properties of natural and synthesized indole compounds showed that they both possess similar and beneficial antidiabetic effects [157]. A series of indole-based compounds were studied for their effects against pancreatic α-amylase and intestinal α-glucosidase properties. All of them showed reported good to moderate α-amylase and α-glucosidase inhibitory effects compared to the standard antidiabetic acarbose [158].

Due to its bioavailability, unique properties and pharmacological potency, indole is regarded as one of the most promising scaffolds for anticancer drug research. This is shown by the U.S. Food and Drug Administration (FDA) approval of some indole-based anticancer drugs like Panobinostat, alectinib, sunitinib, osimertinib, anlotinib and nintedanib for clinical use in addition to several other indole alkaloids conventional chemotherapeutics like vincristine and vinblastine [159,160].

A review of literatures on indole derivatives with promising anti breast cancer effects was carried out. Results showed that indoles derivatives have significant activity against breast cancer. Their mechanisms of action include aromatase inhibition, tubulin inhibition, microtubule inhibition, topoisomerase inhibition, targeting estrogen receptor, DNA-binding mechanism, apoptosis induction, inhibition of PI3K/Akt/NFkB/mTOR, and HDAC inhibition [161].

3. Allyl Sulfides: these are bioactive organosulfur phytochemicals, found as metabolic products of sulfur-containing foods like garlic, onion, and other members of the genus Allium. Allyl sulfide is responsible for the garlic odour. Examples include allyl methyl sulfides, diallyl sulfides, diallyl disulfide, diallyl trisulfides.

These compounds have known wide range of biological activities which include antibacterial, antiangiogenesis, anticancer, anticoagulation, apoptosis and cytotoxicity inducers, antimetastatic etc [162].

They have reported potent antidiabetic and anticancer dual effects [163-170].

Other Antidiabetic – Anticancer Dual - Active Phytochemicals and Phytonutrients

1. Betalains: these are water – soluble nitrogen – containing tyrosine derived pigments made up of red – violet betacyanins and yellow – orange betaxanthins, found in plants (beets) where these have replaced the anthocyanin pigments.

They have various pharmacological activities which include anticancer, antidiabetic, antihepatitis, antioxidant, antihyperlipidemic, anti-inflammation, antimicrobial and antimalarial effects [171-173].

Betalains have reported antidiabetic and anticancer dual effects [174-178].

2. Phytates (Phytic Acid): is a natural antioxidant called inositol hexaphosphate or inositol polyphosphate, found majorly in grains, nuts and seeds. This acid is primarily the way phosphorous is stored in plants. It is commonly referred to as antinutrient because it can bind to dietary nutrients like phosphorous, iron, zinc, copper, manganese, calcium, magnesium etc and decrease their intestinal absorption. The antinutrient effects though problematic for anemic patients, has positive roles in protection against cardiovascular diseases (atherosclerosis), cancer (antioxidant, reduce chemotherapy side effects), diabetes (prevention of free radicals, decrease glycemic response), renal stones (calcium chelation), poisoning (heavy metal chelation) etc.

Phytic acids have reported antidiabetic and anticancer [179-183].

3. Phytosterols: these are plant derived steroids (plant sterols and stanols) structurally related to cholesterol. Both cholesterol and phytosterols are members of the triterpenes family. Phytosterols are found in whole grains, fruits, nuts, legumes and vegetables; their richest sources are vegetable oils and products. Phytosterols have potent and significant cholesterol lowering properties, by inhibiting cholesterol absorption and synthesis.

Several studies have concluded that dietary intake of 2g/day of phytosterols lowers LDL-cholesterol by 10% [184,185]. Structure – specific effects of individual phytosterol constituents showed that saturated phytosterols are more efficient than unsaturated ones in reducing cholesterol levels [186].

Phytosterols have reported antidiabetic and anticancer [187-193].

4. Polysaccharides: these are macromolecular compounds that are made up of various identical (homo eg cellulose, chitin) or different (hetero eg heparin, gamma globulins) monosaccharides with α- or β-glycosidic bonds. They can be storage (starch and glycogen) or structural (cellulose, lignin) in function.

The wide range pharmacological properties of polysaccharides include immunomodulatory, antitumor, anti-inflammatory, antihypertensive, antihyperlipidemic, antioxidant and antimicrobial [194]. Many polysaccharides are effective for metabolic diseases like CVD, diabetes, obesity and neurological diseases, which are usually caused by metabolic disorder of fat, sugar, and protein [195].

Plants polysaccharides have reported antidiabetic and anticancer [196-201].

5. Peptides and Polypeptides: while peptides are chains of less than 50 amino acids, polypeptides are more than 50 amino acids bound together through covalent peptide bond.
Plant polypeptides are formed by hydrolysis of plant proteins under certain conditions. Examples of plant polypeptides include oligopeptides, cyclic peptides, cyclic peptide alkaloids, glycopeptides etc [202].

Plant polypeptides have various wide ranging pharmacological effects like antitumor, antioxidant, antibacterial, hypoglycemic, blood pressure lowering, lipid lowering, etc [202].

Plants peptides and polypeptides have reported antidiabetic and anticancer dual effects [203-207].

6. Protease Inhibitors: these are small molecular weight proteins which inhibit proteases, and play important roles in plant defense systems.

In vitro and In vivo studies have shown protease inhibitors diverse pharmacological potentials in treating various disease conditions like obesity, CVDs, autoimmune diseases, and various cancers (gastric, colorectal, breast, and lung cancers) [208].

Plants Protease inhibitors have reported antidiabetic and varying pro and opposing, cancer and anticancer effects [209-212].

7. Plants Alkaloids: These are nitrogen – containing natural plant products. They are extremely diverse and one of the largest classes of plant secondary metabolites, involved in plant defense systems and very effective in this regards due to their toxicity. They are divided into true alkaloids, pseudoalkaloids, protoalkaloids, peptides and polyamine alkaloids. Examples include morphine, strychnine, quinine, quinidine, caffeine, ergotamine, vincristine, nicotine, emetine, ephedrine, adrenaline.

Alkaloid concentration in plant parts varies depending on the plant. The highest concentrations are in leaves (black henbane), fruits or seeds (Strychnine), root (Rauvolfia serpentina) or back (cinchona) [213].

Alkaloid biosynthetic pathways involves many chemical modifications during their conversion process. These chemical reactions include glycosylation, acylation, reduction, oxidation, and methylation steps, and these confer the pharmacological properties exhibited by the alkaloids [214].

A comprehensive review of the biological effects of glycoalkaloids and their aglycones of the Solanum species, reported their anticancer, anticholesterol, antimicrobial, anti-inflammatory, antinociceptive, antipyretic, toxicity and synergism properties [215]. Plants alkaloids have reported antidiabetic and anticancer dual effects [216-220].

SN	PHYTOCHEMICALS	PLANT SOURCES	MECHANISM OF ACTION AND ROLES.
1	Flavonoids (Flavanol, Flavonol, Flavones, Isoflavones, Flavanones, Anthocyanins)	Fruits (Citrus), vegetables (onion, tomato), grains, barks, roots, stem, flowers, tea and wine.	Antioxidant. Decrease carbohydrates absorption, increase glucose uptake, decrease tissue gluconeogenesis, activates insulin secretion. Decrease advanced glycation end products precursors, sorbitol and pro-inflammatory cytokines. Mediate intracellular and extracellular targets that are involved in cell signaling pathways (Wnt/β-catenin, p53, PI3K. Akt, JAK/STAT, MAPK, apoptosis, NF-Kb) which then modulate cancer proliferation like apoptosis, cell cycle, invasion, metastasis, angiogenesis.
2	Lignans eg Pinoresinol, secoisolariciresinol, matairesinol, podophyllotoxin	Fruits, vegetables, whole grains, legumes and seeds of plants. Cruciferous vegetables, flaxseeds, sesame, berries, pumpkins, brussel sprouts.	Antioxidant, Antidiabetic, α-glucosidase inhibition. Cytotoxic, decrease tumor volume, expression of estrogen, insulin growth factor, progesterone, VEGF and MMP-2, and increased expression of caspase – 3.
3	Phenolic Acids eg salicylic acid, vanillic acid, syringic acid, gallic acid, ellagic acid, p-coumaric acid, caffeic acid.	Fruits (berries), vegetables, cereals, seeds and beverages.	Antioxidant. Increase glucose uptake and glycogen synthesis, and enhance glucose and lipid profiles. Chemopreventive and chemotherapeutic
4	Stilbenes eg Resveratrol, Piceatannol, Pterostilbenes	Grapes (skin), red wine, peanuts and berries.	Antioxidant. Hypolipidemic, hypoglycemic, antiobesity, antidiabetic, antiaging, anticancer
5	Terpenes (Mono, Di, Tri, Tetra terpenes) eg Limonene, cafestol and kahweol, ursolic and oleanolic acids, carotenoids.	Fruits (Orange, grapes), vegetables, coffee, spices and herbs.	Antioxidant. Inhibit the formation of advanced glycated end products. Prevent macular degeneration ad retinopathy. Apoptotic, cell cycle impairment, autophagy, necroptosis.
6	Organosulfur compounds eg Thiols (Glutathione), Glucosinolate (Sulphuraphane), Indoles.	Allium (garlic, onion, chive, leek), cruciferous vegetables, other vegetables (like spinach, tomatoes, carrots, potatoes, mustards), fruits (avocardo, watermelon, pineapple) and cereals.	Increase serum insulin level, enhance HOMA-β index, reduced fasting blood glucose, total cholesterol, LDL-C, and FGF 21 level. Increase liver antioxidant abilities, reduced serum lipopolysaccharide levels. Antiangiogenesis, anticancer, anticoagulation, apoptosis and cytotoxicity inducers, antimetastatic.

Table 1: Showing Summary of Antidiabetic-Anticancer Dual-Active Phytochemicals

Bifunctional Pytochemicals: Alternatives or Adjuncts to Conventional Antidiabetic/Anticancer Drugs

The use of natural plant extracts and their bioactive products as complementary and alternative medicines, in the management of chronic illness like diabetes and cancer, has increased in recent years. Some of these products have reported higher, lower or similar pharmacological properties compared to the conventional drugs. A review of some of these phytochemicals and their potentials as monotherapeutic or combinational agents in treatment regimen is given below.

1. Phytochemicals Reported Pharmacological Properties Compared to Conventional Antidiabetics:

Quercetin is a flavonol sub-group of flavonoids with potent antidiabetic properties. In comparison to conventional synthetic drugs, with many adverse effects, quercetin proved to be exceptional model for the development of new antidiabetic drugs [221]. The effects of quercetin on decreasing plasma glucose, insulin, IL-6, TNF-α, TBAR, and increasing GLUT-4 expression and antioxidant enzymes activities, in skeletal muscle and adipose tissues of diabetic rats, were more significant than that of metformin on all parameters, except for HOMA-IR (similar for both) [222]. However, the combination of quercetin and metformin produces very significant improvement in all the parameters compared to each alone [222,223].

Hesperedin and Hesperitin are both flavanones subgroup of flavonoids. Both phytochemicals equally activated glucose uptake in L6 myotubes after short- and long-term treatment. The percentage of 2-NBDG uptake by both compounds was comparable to that of Rosiglitazone, a known antidiabetic [30].

Naringenin another flavanone has been shown to have similar antidiabetic properties and mechanisms of actions like metformin through its effects on gluconeogenesis and upregulation of AMPK. Naringenin equally has non-glycemic effects like metformin, with similar anti-dyslipidemic, antiatherogenic, anti-inflammatory and antineoplastic properties [224].

Baicalein is a flavone, a subgroup of flavonoids. The antidiabetic effect of baicalein and its natural glucuronide baicalin, was compared to the antidiabetic metformin, as potential antiglycation, anti-radical, and anti-α-glucosidase agents. Results showed that baicalein was the most active compound in decreasing glycation, α-glucosidase activity and free radicals out of the 3 agents; baicalin showed similar activities, but did not inhibit the enzyme α-glucosidase [225].

Anthocyanin and metformin combined administration had significant synergistic effect on glucose consumption in HepG2 cells compared to metformin monotherapy. The combined treatment equally was more effective than metformin alone, in normalizing bold glucose, insulin resistance, liver, pancreas and ileum damage, in mouse model [226].

Proanthocyanidin is a flavanol (flavan-3-ol), a subgroup of flavonoids. The potential role of grapeseed proanthocyanidin in regulating postprandial hyperglycemia, was compared with sitagliptin a conventional antidiabetic and a DPP-IV inhibitor. Results showed both proanthocyanidin and sitagliptin significantly improved postprandial hyperglycemia relative to control [56].

Resveratrol is a stilbene, a subgroup of phenolic acids. When compared with rosiglitazone a conventional antidiabetic, on the induction of glyceroneogenic genes (PDK4 and PEPCK) expression in cultured adipose tissue from obese patients. Results showed that rosiglitazone was much more effective in inducing these genes than resveratrol. Combined treatment of both resveratrol and rosiglitazone induced the genes in parallel with reductions in fatty acid to glycerol ratio [227].

Rosiglitazone a PPAR-y agonist has been reported to increase cardiovascular diseases risks [228,229]. A common feature of atherosclerosis is vascular mineralization formed by vascular smooth muscle cells (VSMC), in a manner similar to mineralization in bone. Rosiglitazone stimulated mineralization in cultured human VSMCs. Rosiglitazone-induced oxidative stress correlated with stimulated osteoblast-like differentiation of VSMCs. Treatment of rosiglitazone-supplemented VSMCs cultures with the caloric restriction mimetic and antioxidant resveratrol, inhibited rosiglitazone-induced oxidative stress, osteoblast-like differentiation and mineralization [230].

Thiols belong to organosulfur compounds. A new series of multifunctional benzimidazole thiols were shown to be potent inhibitors of α-glucosidase. Results of bioactivity assessment showed that all of the compounds are much more effective inhibitors of this enzyme compared to acarbose, a conventional antidiabetic agent [142].

Indoles are another group belonging to the organosulfur compounds. A series of indole-based compounds were compared with acarbose a conventional antidiabetic agent, against their inhibition of pancreatic α-amylase and intestinal α-glucosidase. Results showed that all of the indole compounds showed comparable inhibitory effects with acarbose against these enzymes [158].

Saponins are triterpenoids subgroup of terpenes. Saponin extract elicited more potent α-glucosidase and moderate α-amylase inhibitory effects compared to acarbose [129].

2. Phytochemicals Reported Pharmacological Properties Compared to Conventional Anticancer Agents:

Fisetin

Fisetin is a member of flavonol subgroup of flavonoids. Fisetin was first reported in a study to synergize with paclitaxel in invitro model of lung cancer cell A549. In this study, it was equally reported that fisetin synergizes with arsenic trioxide, but not with mitoxantrone and methotrexate in A549 cells [231]. In another study, on the combination of paclitaxel and fisetin on A549 cells, it was reported that paclitaxel alone was more toxic to normal cells, than the combination with fisetin. This shows that fisetin provides protection against paclitaxel-mediated normal cell cytotoxicity [232].

Kaempferol

Kaempferol is a member of flavonol subgroup of flavonoids. Cancer stem cell markers, such as Oct-4, Nanong, ABCB1, and ALDH1A1, were significantly decreased in MCF – 7 cells treated with Kaempferol and docetaxel. in this study, Kaempferol was reported to be more potent anticancer compound than docetaxel. In another study, kaempferol used alone or in combination with cisplatin, was effective in decreasing ovarian cancer cells proliferation. Another research reported that there was significant therapeutic effect, when doxorubicin or cisplatin was used in combination with kaempferol against HCT – 15 and MDA-MB-231 cell lines [233].

Naringenin

Naringenin is a flavanone which are subgroup of flavonoids. Several studies have shown that naringin and naringenin have significant effective synergistic properties with conventional anticancer agents compared to monotherapy. Both, are known to overcome multidrug resistance in cancer cells [42].

Wogonin

Wogonin is a member of flavone subgroup of flavonoids. Wogonin, cisplatin and paclitaxel inhibited the growth of BGC-823, MGC-803, MKN-45 and HGC-27 gastric cancer cells in dose – dependent manner. Wogonin combined with cisplatin or paclitaxel synergistically to inhibit the growth of these cell lines in vitro [234].

Doxorubicin clinical use as an anticancer agent is markedly affected by its significant cardiotoxicity. Wogonin has reported cardiovascular protective properties. In study, Doxorubicin treated rats exhibited series of cardiac destructions. These destructions were ameliorated with wogonin treatment. Further investigation

showed that wogonin antagonized doxorubicin cardiotoxicity by inhibiting the release of cytochrome c, thereby protecting the rat cardiomyocytes from doxorubicin induced apoptosis via caspase activation [235].

Hesperidin

Hesperidin is a flavanone which a flavonoid subgroup. Single treatment of hesperidin exhibited cytotoxic effect against MCF – 7 Doxorubicin resistant breast cancer cell lines. Combination treatment of doxorubicin and hesperidin demonstrated addictive and antagonistic effect. Hesperidin did not increase the apoptotic induction, but reduced the P-glycoprotein expression level through synergistic effect [35].

The effect of natural flavonoids on the cytotoxicity of doxorubicin against human hepatocellular carcinoma cell line HepG2 was investigated. Results showed that apigenin (a flavone) and hesperidin exhibited the strongest effect on the toxicity of doxorubicin. Though, separate treatment with doxorubicin, apigenin and hesperidin alone resulted in significant oxidative DNA damage and double strand breaks, simultaneous treatment of doxorubicin and apigenin, or doxorubicin and hesperidin completely inhibited these damage, and significantly increased doxorubicin cytotoxicity. Thus, showcasing the potentials of flavonoids in chemoembolization [236].

Paclitaxel effectiveness as an anticancer agent is limited by its multi-organ toxicity. Hesperidin protective effect on paclitaxel induced hepatotoxicity and nephrotoxicity was investigated in a study. The findings showed that hesperidin has chemoprotective properties against paclitaxel hepatotoxicity and nephrotoxicity, mediated via reduction of oxidative stress, inflammation, apoptosis and autophagy [237].

Resveratrol

Resveratrol is a member of the stilbene group of phenols. Resveratrol is known to synergize with conventional chemotherapeutics [110]. Resveratrol enhanced the anticancer effects of paclitaxel in HepG2 cells, paclitaxel resistant triple negative MDA-MB-231 cancer cells and NSCLC cell line A549 [238-240]. Resveratrol has equally been reported to enhance doxorubicin chemosensitivity in multidrug-resistant human breast cancer cells; it reversed doxorubicin resistance by inhibiting epithelial-Mesenchymal Transition vis modulating PTEN/Akt signaling pathway in gastric cancer cells; prevented chemoresistance and augmented doxorubicin and cisplatin chemotherapy; and enhanced cytotoxicity of docetaxel and doxorubicin in solid tumor cell line in vitro [241-243].

Sulforaphane

Sulforaphane is an isothiocyanate member of organosulfur compounds. Sulforaphane has reported synergistic and additive effects with several classes of anticancer agents like paclitaxel, docetaxel and gemcitabine [154].

Conclusion

Plants owe their various pharmacological properties to their active phytochemical components, several of which are known to be very protective in human. Some of these phytochemicals have verifiable and established dual antidiabetic and anticancer effects.

This article reviewed several groups of these phytochemicals, with emphasis on their reported preclinical (in vitro and in vivo) and clinical pharmacological effects and mechanism of actions. Their various pharmacological potencies and efficacies were compared with conventional and current antidiabetic and anticancer drugs. These phytochemicals exhibited varying degrees (lower, equal, higher) of comparable pharmacological effects to the conventional agents, in these regards. Some showed potencies as single, synergistic and combined agents with conventional therapies.

It is expected that more researches will be carried out on these phytochemicals to remove the challenges (bioavailability, toxicity profiles, etc.) militating against the prospects of approving these compounds as formal therapeutic drug agents.

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