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Bifunctional Antidiabetic – Anticancer Dual - Active Plants: New Roles, Challenges and Prospects

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Abstract

Plants have played significant roles in the management of diseases in ancient times, and folk medicine. And, they still play large roles among natives in rural communities and in parts of Africa and Asia.

Up to 60% of drugs in use today have their origin to plants and natural products. Several of the known plants used for management of various ailments in the past have reported wide ranges of pharmacological effects which include antioxidant, anti-inflammatory, antimicrobial, antiallergic, immunomodulatory etc. effects, due to their multiple bioactive phytochemical constituents.

Some of these plants equally exert dual-effect antidiabetic-anticancer activities by affecting processes and pathways common to both diseases viz. antioxidant, anti-inflammation, anti-hyperglycemia, increase in insulin sensitivity, decrease in insulin resistance and modulation of diabetes-cancer common and related signal transduction pathways.

They equally exert direct antidiabetic and anticancer effects by inhibiting enzymes involved in glucose metabolism, and mediating anti-tumor processes like apoptosis, antiproliferation, antimigration, antimitosis, antiangiogenesis etc. These plants have been shown to be effective either as monotherapy or in combination with conventional therapies where they exert synergistic properties and increased activities.

This article reviewed several plants with reported proven and potential dual-effective antidiabetic-anticancer properties , their bioactive constituents and pharmacological processes, their reported in vitro and in vivo studies, and proffer insights on their new roles, challenges and prospects.

Keywords: Bifunctional Antidiabetic-Anticancer, Phytochemicals, Bioactive Constituents.

1. Introduction

The pharmacological properties and potencies of plants have been known to man time immemorial. This is not a surprise as many drugs and pharmaceutical agents have their origins from natural plants, hence the special field of pharmacology known as pharmacognosy and its linked ethnopharmacology. Some of these plants are known to have several ranges of pharmacological properties and efficacies which include antidiabetic, anticancer, antibiotic, anti-inflammatory, antioxidant, antiallergic, etc effects.

Several plants have antidiabetic and anticancer dual-effect proven capabilities. Examples include: Garden egg (Solanum melongena), Bitter leaf (Vernonia amygdalina), Garlic (Allium sativa) and Onion (Allium cepa), Ginger (Zingiber officinale), Citrus genus, Aloe Vera (Aloe barbadensis), Sweet wormwood (Artemisia Annua) etc. These plants exercise these dual - effects due to the presence of multiple therapeutically active phytochemicals in their fruits, seeds, leaves, stems, barks and roots etc.

A review of 104 plants with proven antidiabetic effects in their root extracts showed that flavonoids, phenolic compounds, alkaloids and phytosteroids are the most abundant natural compounds in plants roots with antidiabetic effects [1]. It is estimated that 50 – 60% of cancer patients in the United States use anticancer agents derived from different parts of plants alone or combined with conventional anticancer treatments like chemotherapy and/or radiotherapy. These agents include curcumin from turmeric, genistein from soybean, tea polyphenols from green tea, resveratrol from grapes, sulforaphane from broccoli, isothiocyanates from cruciferous vegetables, silymarin from milk thistle, diallyl sulfide from garlic, lycopene from tomato, rosmarinic acid from rosemary, apigenin from parsley, gingerol from ginger etc [2].

Natural plants have to their advantages fewer side effects, cost effective, availability, easy accessibility, new cellular targets, novel molecular therapeutics and multiple health benefits compared to conventional antidiabetics and anticancer agents.

The aim of this review is to describe the antidiabetic and anticancer dual-roles of these plants and highlight their importance in the management of diabetic patients with concurrent cancer

illness and cancer patients with glucose intolerance. This review also aims to highlight developmental challenges facing the clinical use of these plants, their recent therapeutic advances and the prospects and future roles of these plants in diabetes and cancer managements.

1. 1 Bifunctional Plants With Dual Antidiabetic – Anticancer Effects

1. Solanum Genus: The Eggplant is member of the Solanum genus of Solanaceae family. This genus equally includes other useful plants like tomato and potato. Plant species from the genus are known to modify complications of diabetes like hyperlipidemia and oxidative stress in animals [3]. Glycoalkaloids extracts from solanum plants include solanine, chaconine, solasonine, solamargine and tomatine exhibit anticancer activities alone and in combination with chemotherapeutics. They possess antiproliferation, anti-migration, apoptosis anticancer, anti-angiogenesis efficacies and act through various molecular and signal transduction pathways [4].

a) Garden Egg or Eggplant (Solanum Melongena, Solanum Aethiopicum): The Eggplant is a rich source of phenolic and alkaloid compounds. It has several therapeutic properties like antioxidant, antidiabetic, anticancer, antihyperlipidemic, antihypertensive, etc. supported by several studies. Eggplant antidiabetic effect is mediated via antioxidative roles and inhibition of α-amylase and α-glucosidase enzymes [5].

A comparative study on the aqueous extracts of leaves and fruits of eggplant, negative control, and positive control (glibenclamide) on alloxan induced diabetic guinea pigs showed significant difference between the group that had aqueous leave extracts and negative control. The positive control (Glibenclamide) had 60% decrease in the mean fasting blood glucose level, while the group that received aqueous leaf extracts of Solanum melongena had 40% reduction in mean fasting blood glucose level [6].

Methanolic extracts from fruit peels of Solanum melongena showed the presence of bioactive glycoalkaloids Solasonine, Solasodine and Solamargine, which exhibited in vitro cytotoxicity and antiproliferative activities against human liver cancer cell lines (Huh7 and HepG2) via cell cycle arrest at S-phase and apoptosis induction [7].

b) Tomato (Solanum Lycopersicum): Several studies have shown that consumption of tomato juice or extract do not change plasma glucose level in diabetics. However, long-term consumption of tomato by patients with type 2 diabetes led to reduced glycosylated hemoglobin levels, with higher antioxidant enzyme activity and lower lipid peroxidation rates seen after tomato consumption [8,9]. Tomato extract lycopene (90mg/kg body weight) when administered to streptozotocin (STZ) – induced diabetic rats led to reduced fasting glucose level [8,10]. 14.5mg/kg of body weight is the therapeutic dose equivalent of lycopene in human [8,11]. Kaempferol, an antioxidant flavonoid found in tomato, equally reduced plasma glucose to normal when given to STZ-diabetic rats [8]. Obese diabetic mice fed with 13-oxo-9,11-octadecadienoic acid, a potent PPAR-α activator present in processed tomato juice, and an isomer of 9-oxo-10,12-octadecadienoic acid present in fresh tomato, had reduced plasma glucose level [8,12].

72 Epidemiological studies of intake of tomatoes, tomato-based products and blood lycopene level in association to the risk of several cancer were reviewed. 57 of these studies showed inverse relationships between tomato consumption or blood lycopene level and the risk of Cancer at a defined anatomic site; 35 of these inverse relations were found to be statistically significant. None of the studies linked higher intake of tomato or blood lycopene level to statistically significant elevated risk of cancer at the studied sites [13]. Cancers with the biggest evidence of benefit were prostate, lung, and stomach. Others cancers with benefit were pancreas, colon, rectum, esophagus, oral cavity, breast and cervix [13].

c) Irish Potato (Solanum Tuberosum): Potato leaves, tuber, peel and juice have found important use in traditional medicine. The pharmacological properties of potato include antioxidant, anticancer, antiallergy, antibacterial, anti-inflammatory, antiulcer and anti-obesity. Potato contains phenolic acids, anthocyanin, flavonoids, vitamin B6, B3, pantothenic acid [14]. 3 doses of SlendestaTM Potato Extract (SLD) (50, 150 or 300mg/kg) were orally given to obese mice once daily for 28 days. 4 weeks after SLD treatment in obese mice, body weight, food consumption, epididymal fat, serum chemistry, histomorphological changes of fat and pancreas were significantly and dose-dependently reduced compared with the obese control mice [15]. The anticancer effects of Anthocyanins contained in Solanum Tuberosum were studied in breast and hematological cancers. Cellular and molecular investigations of the effect of the anthocyanin extract in cancer cells showed modulation of cell cycle regulators upon treatment. Also, apoptotic factors like TRAIL were enhanced while Akt – mTOR signaling was inhibited in tumor cells leading to maturation of acute myeloid leukemia cells [16].

2. Bitter Leaf (Vernonia Amygdalina): A very popular African herb and a member of daisy family. Bitter leaf has been used by native Africans for centuries to treat many diseases, inflammation and wound. It has equally been used as an antiseptic, pesticide, timber, cash crop, food (soup, stew, tea, salad, juice, drink) and appetite enhancer. It is rich in nutrients like proteins, vitamins, minerals, and β – carotenes that modulate production of female sex hormones, enabling women to stay young and healthy. It is equally rich in glucosides, diterpene, lactones, andrographolide, and flavonoids which are powerful antioxidants.

Vernonia amygdalina (VA) leaves has been used for many years to treat diabetes and this has been confirmed in studies with laboratory animals [17-19]. It has equally been shown that the sequential chloroform extracts rather than the methanol or water extracts of the leaves of VA is more effective in exhibiting antidiabetic effects; and that the predominant fatty and phytanic acids in this fraction played key role in this activity [17,20]. The bioactive compounds extracted from VA include Vernodalin, Vernomygdin, Vernoniosides (A1, A2, A3, A4, B1, B2, B3, D and E), Vernodalol and Epivernodalol [17,21].

Some studies showed that administration of VA extract led to regeneration of the β – cells of the pancreas and thus responsible in part for its antidiabetic activity [17,19,22]. Histochemical analysis of the leaf of VA showed presence of acidic lipid, mucilage, pectin, lipids, polyphenols and alkaloids. HPLC analysis of the leaves hot water infusion showed the presence of quercetin and (-)-epi-catechin [23]. The infusion showed potent 2,2-diphenyl-1-picrylhydrazyl scavenging effect and ferric reducing antioxidant ability; and also, ability to elevate glutathione level, superoxide dismutase and catalase activities, and at the same time reducing malondialdehyde level and DNA fragmentation in Fe2+ -induced hepatic injury [23]. The infusion significantly inhibited α-glucosidase and pancreatic lipase. It equally inhibited intestinal glucose absorption and enhanced muscle glucose uptake [23].

200mg/kg and 400mg/kg body weight chloroform extract of VA and metformin (500mg/kg) were administered to Streptozotocin induced diabetic rats (SDRs) for 7 and 14 days, in a study to determine the mechanism of action of VA. The 14 – day regimen of 200mg/kg and 400mg/kg extract and metformin (500mg/kg) showed significant reduction in the expression of gluconeogenesis enzymes: Fructose 1, 6-Bisphosphatase, Phosphoenol pyruvate carboxikinase and Glucose 6-phosphatase in the liver and muscle compared to diabetic control; and also, significant elevated expression of glucose 6-phosphate dehydrogenase (G6PDH) gene in the liver [17].

A systematic review of studies on VA anticancer effects published from January 2000 to November 2018 revealed that VA inhibits cell viability, DNA synthesis, and causes DNA damage in cancer cells in time and concentration dependent manner. VA equally induces apoptosis and cell cycle arrest in tumor cells through gene regulation [24]. Studies showed that low concentrations of water-soluble leaf extracts of VA retarded the proliferation of ER+ Human breast cancer cells (MCF-7) in vitro in a concentration-dependent manner. Treatment of BT-549 (A human triple negative breast cancer cell line obtained from papillary invasive ductal cancer, and known to be insensitive to 10 and 100nM paclitaxel treatments) to increasing concentrations of VA (10, 100 and 1000µg/mL) Inhibited cell growth by 14% ($p<0.05$), 22% ($p<0.05$) and 50% ($p<0.005$) respectively, and DNA synthesis by 22%, 76% ($p<0.05$) and 86% ($p<0.01$) respectively [25].

Ethanol extract and VA silver nanoparticles inhibited MCF-7 cell proliferation with half-maximal inhibitory concentration (IC50) value of 67µg/mL and 6.11µg/mL respectively, following 72hr of treatment. The ethanol extract and VA silver nanoparticles equally caused G1 phase cell cycle arrest, enhanced apoptosis and nuclear fragmentation in MCF – 7 cells [26].

3. Neem (Azadirachta Indica): native of india and tropical / subtropical regions, neem is of the mahogany (Meliaceae) family, and has been used for its powerful medicinal properties for thousands of years. The various part of this plant viz barks, leaves, sap, fruits, twigs, seeds and seed oil have potent and versatile therapeutic metabolic and anticancer uses.

Neem tree is the world's most studied tree and one of the most promising in the 21st century. Neem is an important source of flavonoids, terpenoids, tannins, saponin, anthraquinones, sterols, and alkaloids which are very important in diabetes control. Neem derivatives like rutin and quercetin demonstrated hypoglycemic properties while nimdin is important in weight control [27].

Over 140 different bioactive compounds have been isolated from neem with at least 35 of these demonstrating significant tumor suppression by interfering with the carcinogenesis process; these include: nimbin, nimbidin, nimbolide and limonoids. The first polyphenolic flavonoids derived from neem leaves were quercetin and β – sitosterol which have antitumor, antioxidant and apoptotic properties [28].

Diabetic rats showed impaired glucose tolerance and insulin signaling molecules. 400mg/kg Oral effective dose of A. indica was administered once daily for 30 days to high – fat diet - induced diabetic rats. Result showed normalized blood glucose, serum insulin. Lipid profile and insulin signaling molecules, as well as GLUT 4 proteins [29].

A systematic review of literatures on the anticancer properties of neem sowed that the anticancer activities of neem is mediated through its hepatic antioxidant effects as well as oncostatic induction through several mechanisms like: suppression of the NF – kβ pathways, enhanced tumor suppressor genes expression, inhibition of oncogenes expression and increased apoptosis [30].

4. Citrus genus: Examples include sweet orange (Citrus sinensis), Sour orange (C. aurantium), lemon (C. limon), lime (C. aurantiifolia), grapefruit (C. paradisi), tangerine (C. reticulata), citron (C. medica), pomelo (C. maxima) etc.

Citrus, genus of plants in the rue family, Rutaceae is known to have both antidiabetic and anticancer properties [31,32]. Citrus genus is very rich in vitamin C and phytochemicals (carotenoids, polyphenols, phenolic acids, flavonoids, coumarin, terpenoids, saponin, stilbenes, lignans etc) which enhance their various anti-inflammatory, antibacterial, anticancer, antidiabetic etc activities [33,34].

Citrus peel extracts (CPEs) containing flavonoids are known to possess antiproliferation, antiangiogenesis, anti -metastatic, anti- inflammatory and apoptotic effects [35].

Methanol seed extract of Citrus paradisi at 100, 300 and 600mg/kg/day dissolved in10mg/kg DMSO administered for 30 days in male Wistar rats resulted in dose related reduction in fasting blood glucose, cardiovascular risk factors and lipid profiles [36].

Navel orange was found to have nutraceutical value in diabetes management. Flavonoids identified in the extract were found to have antioxidant, α-glucosidase inhibition and antiglycated activities [37]. Orange peel extracts given to alloxan induced diabetic rats at 125, 250 and 500mg/kg body weight respectively decreased the blood glucose and cholesterol values in dose dependent manner [38].

Ethanol extracts of lime, tangerine, orange and grapefruit anticancer and toxicity effects were investigated against two hormone sensitive breast cancer cell lines MCF-7 and T47D, and normal human HFB4 cells. The CPEs showed significant selective anticancer effects against the MCF-7 and T47D cell lines [39].

Furanocoumarin and flavonoid components of grapefruit are known to inhibit cytochrome P450 3A4, the enzyme responsible for metabolizing about 50% of drugs in the liver and small intestine, causing about 85 drug-drug interactions [40].

5. Sweet Wormwood (Artemisia Annua): an annual plant in Artemisia genus of the daisy (Asteraceae, Sunflower or composite) family, with origin in south east Asia and used in China traditional medicine for thousands of years. Artemisinin, a popular effective antimalaria also known as qinghaosu in China is a sesquiterpene endoperoxide bioactive extract derivative of Artemisia annua. Species from the artemisia genus are equally known to have potent anticancer, antidiabetic, antioxidant, anti – inflammatory and antibiotic effects.

A systematic review of 14 studies of Artemisia species on diabetic animals and humans published between 2000 and April, 2017 clearly revealed that single or multiple doses of both the aqueous and alcoholic extracts of Artemisia resulted in significant hypoglycemic effects in alloxan, Streptozotocin and high fat diet induced diabetic animals, and diabetic humans [41].

Polar fraction of Artemisia annua L. leaves demonstrated antidiabetic effects in vivo. The antidiabetic effects of 3 main compounds isolated from this fraction viz 3, 5 – dicaffeoylquinic acid, 4, 5 – dicaffeoylquinic acid and 3, 4 – dicaffeoylquinic acid methyl ester, were studied using several in vitro enzyme inhibition assays. Results showed that these dicaffeoylquinic acids inhibited dipeptidyl peptidase IV, α – glucosidase, α – amylase and aldose reductase enzymes and exerted potent antioxidant effects [42]. The antidiabetic effects of Artemisia annua and artemisia afra herbal tea were investigated on 5 diabetic patients in large scale clinical trials (that also included tests for efficacy against malaria and schistosomiasis). Results showed that Artemisia annua and Artemisia afra infusions demonstrated high therapeutic efficacy against diabetes with no observable side effects, and with blood glucose lowered to standard level, confirming previous trials in animals [43].

The antidiabetic effect of Artemisia is attributed to its polytherapy properties. Artemether was reported to transdifferentiate α -cells to β – cells by a European consortium in 2017, however, the finding was challenged by other studies. A very recent study in 2022 confirmed that artemether and another sesquiterpene, aspterric acid, induced α – cell transdifferentiation to β – cells, both in zebra fish and in ATC1-6 cells [43,44]. Arachidonic acid increases insulin secretion and sensitivity and inhibit enzymes that activate human β – cell destruction. Artemisia genus is known to contain very high concentration of arachidonic acids [43]. Artemisia plants are rich in Anthocyanins and Proanthocyanidins which are known to protect and regenerate β – cells [43]. Artemisia are equally very rich in arginine, chlorogenic acid, caffeoylquinic acids, saponins, thujone and pentacyclic triterpenes which are known to possess potent antidiabetic properties [43].

Artemisia annua extract, enhanced by acetonitrile, inhibited the viability of breast (MDA-MB-231 and MCF – 7), pancreas (MIA PaCa-2), prostate (PC-3), NSCLC (AA459) cells. Also, the extract's richest constituents, chrysosplenol D, arteannuin B and casticin (but not arteannuic acid or 6, 7 – dimethoxycoumarin) inhibited MDA-MB-231 breast cancer cells [45]. The extract activated the accumulation of multinucleated cancer cells within 24 hr of treatment, increased the number of cells in S and G2/M phase of cell cycle and activated caspase 3 [45]. Cancer cells sequester iron and store up to 1000 times more than normal cells. Artemisinin has potent antioxidant effects and creates highly reactive free radicals by the breakdown of 2 oxygen atoms that destroy cancer cells via the process of ferroptosis [46]. Artemisinin sensitizes cancer cells to ferroptosis, a form of programmed cell death through iron-dependent lipid peroxidation. Dihydroartemisinin activates lysosomal breakdown of ferritin in an autophagy-independent manner, increasing iron concentration in cells and making cells to be more sensitive to ferroptosis [47].

Artemisinin equally exerts pleiotropic antiproliferative effects in cancer cells through may pathways like angiogenesis inhibition, apoptosis, cell cycle arrest, cell migration arrest and regulation of nuclear receptor response. Unlike chemotherapy which is equally toxic to normal cells, artemisinin showed no significant toxicity in normal cells in over 4000 studies [46].

Artemisinin has targeted cytotoxic properties in vitro and in vivo against multiple drugs- and radiotherapy- resistant cancer cell lines, due to the fact that most cancer cells express high concentration of transferrin receptors on their cell surfaces that is responsible for the sequestration and storage of iron ion much more than normal cells [48]. Artemisinin conjugation to transferrin through carbohydrate chain has equally proved to be highly effective and specific with targeted delivery of artemisinin to cancer cells [48].

6. Aloe Vera (Aloe barbadensis, Aloe indica, Aloe africana): is a juicy perennial herb of the Aloe genus and Liliaceae or Asphodelaceae family and is one of the most used plant in the world. It has its origin from the Arabian Peninsula and Africa, but is equally cultivated in subtropical regions of the world. Its earliest documented use is in ancient Egypt about 6, 000 years ago, where it was called ''the plant of immortality" and used to treat various skin conditions like sunburn, rashes, burns, sores, ulcers, wounds, and also for make-up purposes. It was said to have been used by Cleopatra 2, 000 years ago as part of her beauty regimen.

Aloe vera also has other proven therapeutic effects like anticancer, antidiabetic, antioxidant, and antihyperlipidemic [49]. Aloe vera has more than 75 bioactive constituents which includes vitamins (A, C, E and B12), enzymes (Amylase, catalase, peroxidase), minerals (zinc, copper, selenium, calcium), anthraqui-

nones (aloin and emodin), sugars (monosaccharides and polysaccharides), fatty acids (lupeol and campesterol), hormones (auxins and gibberellins), and others (salicylic acid, lignin and saponin) [49].

Aloe vera methanol extract (AVM) significantly reduced the formation of advanced glycation end-products (AGEs), as well as fructosamine, carboxymethyl lysine and carbonyl protein in BSA/glucose assay. AVM equally significantly inhibited α-amylase and α-glucosidase enzymes [50]. In a clinical trial to evaluate the antidiabetic efficacy of oral administration of Aloe vera, patients with diabetes were given one tablespoon of Aloe vera juice, twice a day for at least 2 weeks. Results showed that the blood sugar and triglyceride levels in the treated group were reduced, while cholesterol level were unaffected [51]. The bioactive constituents of Aloe vera have been shown to work in different pathways to effect antidiabetic control and their synergistic properties significantly enhances the antidiabetic efficacy of Aloe vera. Different groups of diabetic rats were fed with Aloe vera extract, Carbohydrate fraction and Peptide/polypeptide fraction, for 3 weeks. The rats fed with Aloe vera extract and its 2 fractions had their glucose and insulin levels restored to normal. Further proteomic analysis showed that carbohydrate fraction increased glucose uptake and decrease oxidative stress, while the polypeptide fraction acts on the incretin pathway by reducing zonulin levels hence, restoring intestinal permeability [52].

A systematic review of studies on the anticancer effects of Aloe vera revealed that Aloe vera contain anticancer bioactive constituents like: Aloin, a natural anthracycline active against breast cancer cells (more effective against ERBB -ve than ERBB +ve breast cancer cells); Emodin, a natural anthraquinone effective against myeloma and pancreatic cancer cells (Emodin Azide Methyl Anthraquinone Derivative block phosphorylation of Her2/neu, suppress growth, transformation and metastasis as tyrosine kinase inhibitor); Aloe-emodin, a natural hydroxyanthraquinone effective against colon, oral, gastric, colorectal, cervical, lung, prostate, NPC and hepatocellular carcinoma cells [53].

Alomicin effective against hepatoma; Alomicin and Aloe mannan effective against sarcoma; Aloesin inhibit ovarian cancers [53].

The anticancer effect of Aloe vera is due majorly to two separate mechanisms: antiproliferative, effected via Aloe latex and immune-stimulatory, due to Aloe polysaccharides [54]. Aloe latex is produced in the thin middle layer of Aloe vera leaf and contains glycosylated anthraquinones (Aloin A and Aloin B), glycosylated chromones (Aloesin and Aloeresin), polyphenols, as well as free anthraquinones like Aloe-Emodin as minor constituents [54]. Some in vitro and in vivo research have discovered the potential mutagenic and carcinogenic effects of aloe latex (Aloe-Emodin, Aloin, Aloesaponarin). Hence, the International Aloe Science Council (IASC) advised that the limit of Aloin content should be less than 10ppm in Aloe products made for oral consumption [54]. Cytotoxic effects of Aloe vera crude extract (ACE) alone and in combination with cisplatin were studied in human breast (MCF-7) and cervical (HELa) cancer cells. Exposure of the cells to ACE led to loss of viability in a time – and dose – dependent manner, effected via apoptotic pathways as seen in the changes of nuclear morphology and spread of cells in various phases of the cell cycle. The ACE was found not to have significant cytotoxicity towards normal cells [55].

7. Grapes (Vitis Vinifera, Vitis Labrusca): is a fruit of the grapevine, a perennial vining plant of the Vitis genus in the flowering Vitaceae family. The origin of, and use of grape is as old as man as shown in the Greek mythology, where Dionysus the god of wine was illustrated holding a cluster of grapes. The oldest winery is known to be in Armenia around 4000 BC. The whole fruit, skin, leaves and seed of grape have been known for their medicinal values for thousands of years.

Grapes contains bioactive constituents like phenolic acids, flavonoids, anthocyanins, stilbenes and lipid which are important in their medicinal values. They have antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic properties and have various uses in food and nutraceutical industries [56,57].

The major phenolic constituents in grapes berries are hydroxycinnamic acids, stilbenes (resveratrol), flavonoids (including anthocyanins, proanthocyanidins, quercetin) are powerful antioxidants. Grapes are also rich in phytosterols and fatty acids [56]. Systematic analysis of bioactive constituents of wastes mainly from peels and seeds of 30 grape varieties showed that the antioxidant properties were diverse among the various grape peels and seeds. Different phenolic compounds measured included: gallic acid, cyanidin-3-glucoside, epicatechin, catechin gallate, ferulaic acid, rutin and resveratrol which enhances the antioxidant effects of these grapes [58].

Administration of grape seed extract (GSE) (100mg/kg/day) decreased the lipid peroxides and carbonylated proteins and enhanced the antioxidant activity in plasma and hepatic tissues of streptozotocin induced diabetic rats [59]. In a double-blind randomized, placebo-controlled trial, 32 type 2 diabetes mellitus patients were prescribed diet or oral glucose-lowering agents and received grape seed extract GSE (600mg/day) or placebo for 4 weeks. GSE significantly improved markers of inflammation and glycemia, and a sole marker of oxidative stress in obese type 2 diabetics at high risk of cardiovascular events [60]. Improved insulin resistance was equally reported in adolescents with metabolic syndrome who received 100mg/kg of GSE for 8 weeks [61].

Studies with fresh and fermented pomace extracts of 2 varieties of Vitis vinifera L. viz Feteasca neagra and Pinot noir, showed the fermented extracts had higher polyphenol contents. Fresh extracts have better antioxidant and anti-inflammatory properties in a concentration-dependent manner (since polyphenols can equally be prooxidant). But, the fermented extracts had more effective and significantly higher antiproliferation effects than the fresh extracts against human lung (A549), Breast (MDA-MB-231), murine melanoma (B164A5) cell lines, due to their higher polyphenol contents [62].

In another study, the cytotoxic effects of methanol extracts of fruits and leaves from both virus-free and virus-infected Vitis vinifera were investigated against MDAMB-231 breast cancer cell line and HEK 293 human embryonic kidney normal cell line. Results showed that the various methanol extracts of the virus-infected (grapevine fanleaf virus) leaf, skin and seed showed more potent cytotoxic effects against MDA-MB-231 and HEK 293 cells, compared with the healthy Vitis vinifera, due to the higher polyphenol content in the infected variety [63]. The cytotoxicity of extracts from the older leaves were equally found to be more potent than the younger leaves varieties, for the same reason [63].

Grape seed extract (GSE) is a rich source of proanthocyanidins a class of polyphenols effective against colorectal cancer. GSE (25-100microg/ml) caused a significant in vitro time- and dose-dependent inhibition of human colorectal cancer HT29 and LoVo cell growth and cell deaths mainly through apoptosis and caspase -3-activation. In vivo oral (200mg/kg dose) GSE feeding to athymic nude mice with HT29 tumor xenograft analyzed with immunohistochemistry showed time- dependent inhibition of tumor [64]. In vitro use of biosynthesized silver nanoparticle of Vitis vinifera (Vv-AgNP) combined with 5-FU significantly increased their cytotoxic, antiproliferative, apoptotic and oxidative effects against HT-29 cell line [65].

8. Allium Genus: this includes well known garlic and onions, perennial plants of Amaryllidaceae family, with origin in central Asia.

a) Garlic (Allium Sativum): is among the oldest known plants used for flavoring and seasoning food.

Garlic has various bioactive constituents like allicin, alliin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, and S-allyl-cysteine. Garlic and its bioactive compounds possess antioxidant, anti-inflammatory, antibacterial, antifungal, immunomodulatory, anticancer, antidiabetic, anti-obesity, etc. activities [66].

A review of articles on the importance of garlic in the management of diabetes and diabetes-associated comorbidities showed that Garlic and its active constituents in vitro and in vivo demonstrated significant hypoglycemic effects and reduction of insulin resistance [67]. Oral administration of garlic extract (0.1, 0.25 and 0.5g/kg body wt) for 14 days was studied in normal and streptozotocin-induced diabetic rats. Results showed that garlic extract significantly reduced serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, AST and ALT levels, while increasing serum insulin levels in diabetic rats, but not in normal rats [68]. When compared with Glibenclamide (600µg/kg) a conventional antidiabetic, the antidiabetic activity of the garlic extract was found to be more effective [68].

In vitro and in vivo studies have shown that garlic and its bioactive organosulfur constituents exhibit significant anticancer effects through apoptosis, antiproliferation, free radical scavenging, enhancing antioxidant glutathione S-transferase enzymes, and decreasing tumor size [69]. Garlic extract, its phytocompounds and nanoformulations are known to suppress various stages of tumor including initiation, promotion and progression. The bioactive compounds changes lipid peroxidation, nitric oxide synthase effect, nuclear factor-kB, EGFR and protein kinase C [70]. Several studies have shown that Allium sativum and its organosulfur constituents decreases the risk of breast, larynx, colon, skin, endometrial, esophageal, bladder and lung cancers with proven anticancer effects in breast and prostate cancers [71-75].

b) Onion (Allium Cepa): herbaceous biennial plant, is the most widely cultivated species of the Allium genus.

Allium cepa is one of the most commonly used condiment and seasoning plants in the world. Its therapeutic properties are attributed to its bioactive contents like quercetin, thiosulphinates and phenolic acids. A review of articles on its pharmacological and therapeutic activities from various studies showed that onion has significant anticancer, antidiabetic, and antiplatelet properties [76].

Allium cepa increased fasting serum HDL levels with hypoglycemic and hypolipidemic effects associated with antioxidant and reduced superoxide dismutase effects in Streptozotocin (STZ) induced diabetic rats [77].

In a biochemical study, Alloxan was given as a single dose (120mg/kg body wt) to induce diabetes in rats. 1ml of either onion or garlic juices /100g body wt dose was given orally daily to these alloxan-induced diabetic rats for 4 weeks. Results showed that treatment with either garlic or onion juices restored elevated plasma levels and decreased liver activities of glucose, urea, creatinine, bilirubin, AST, ALT, LDH, alkaline and acid phosphatases (ALP and ACP) in diabetic rats to their normal levels [78]. Also, restored to normal levels with the treatment, are the increased concentration of thiobarbituric acid reactive substances and activity of glutathione S-transferase in plasma, liver, testes, brain and kidney of the diabetic rats [78].

Systematic Meta -analysis of the antidiabetic activities of onion and garlic in diabetic rats was carried out using 10 literatures. The treated diabetic rats were supplemented with either onion or garlic extracts or with single constituents, including S-methylcysteine sulfoxide, S-allylcysteine sulfoxide and diallyl trisulfide. The antidiabetic effects of onion extract and single constituents were significant for glucose concentration and body weight ($p<0.05$), while the effects of garlic extract were not significant [79].

Epidemiological studies link Allium genus, which includes garlic, onions, shallots, leeks and chives, consumption to decrease in especially gastrointestinal cancers [80,81]. The potential anticancer mechanism of the extracts from these vegetables includes bioactivation of carcinogens, antimicrobial activities and redox modification; and they and their constituents are known to have effects at each stage of carcinogenesis [80].

The link between the rate of onion (Allium cepa) and garlic (Allium sativum) use and cancer at several sites were investigated using data from integrated network of Italian and Swiss case-control studies. The odd ratios (ORs) were calculated using

multivariate logistic regression models which were corrected for energy intake and other covariates [82]. The multivariate ORs for the maximal category of onion and garlic intake were, respectively, 0.16 and 0.61 for cancer of oral cavity and pharynx, 012 and 0.43 for esophageal cancer, 0.44 and 0.74 for colorectal cancer, 0.17 and 0.56 for laryngeal cancer, 0.75 and 0.90 for breast cancer, 0.27 and 0.78 for ovarian cancer, 0.29 and 0.81 for prostate cancer and 0.62 and 0.69 for renal cancer; showing an inverse relationship between rates of use of Allium cepa and Allium sativum and the risk of various common cancers [82]. Notice, that onion (Allium cepa) had lower ORs in each and all of the studied cancers compared to Garlic (Allium sativum), similar to what was obtained in their antidiabetic study above.

9. Mistletoe (Viscum Album, Phoradendron Serotinum): This is a large group of parasitic, evergreen, perennial flowering plant of 4 families, 8 genera and about 450 species, native to Europe and America. It is very popular in ancient legends, folklores and mythology and has been known for its healing powers for thousands of years. Mistletoe is equally known for its poisonous and toxic effects due to its phoratoxin bioactive constituent.

Mistletoe has many and different groups of bioactive constituents responsible for its varied, complex and cross-system pharmacological properties and these include: mistletoe lecithins (ML I, II, III), viscotoxins, kuttan's peptides, oligo- and polysaccharides, lipids, flavonoids, thiols, plant acids, phytosterols and sterols, phenylpropanes, lignans, alkaloids, minerals, trace elements, proteins, triterpenes. The contents of the various components depend on the season, age of plant, habitat and host tree [83,84]. Various medicinal properties of mistletoe extracts studied include anticancer, antidiabetic, immunomodulatory, neuropharmacological, cardiac, hepatoprotective, antibacterial, antifungal. This plant modulates related or unrelated targets in many signaling pathways that are effected through membrane receptors, enzymes, ion channels, transporter proteins and transcriptional targets [85].

Viscum album has been known as a traditional therapy for diabetes. 1-10mg/ml aqueous extract of mistletoe elicited a stepwise 1.1 to 12.2-fold activation of insulin secretion from clonal pancreatic β-cells. The insulin-releasing activity of mistletoe extract was not affected by 16.7mM glucose, 1-alanine (10mM), 3-isobutyl-1-methoxyxanthine (IBMX) (1mM), or depolarizing concentration of KCL (25mM) nor was it mediated by lectins. This study showed the presence of insulin-releasing bioactive constituent in Viscum album [86]. The antidiabetic properties of aqueous leaf extract of Viscum album (Guava mistletoe) were compared with conventional metformin antidiabetic using alloxan-induced rat models. Results showed dose-dependent significant decrease in in the serum glucose level in diabetic rats administered mistletoe extract. The effect was more noticeable with mistletoe compared with diabetic control and metformin-treated groups [87].

Viscum album extracts showed immunostimulatory and cytotoxic activities against cancer cells and are used in Europe in adjuvant chemotherapy. Characterization of the active constituents showed Apoptosis-inducing and ribosome-inactivating lectins as well as cytotoxic thionins (viscotoxins) are the main class of constituents mediating mistletoe anticancer effects [88].

Viscum album L. is the medical herb prescribed most often for cancer patients in German-speaking countries; mistletoe extracts are also available as approved drugs. Many clinical studies showed mistletoe extracts to be effective in the management of cancer patients [84].

Aqueous extract Isorel, from fresh mistletoe was found to be very useful in experimental adjuvant chemotherapeutics by increasing the efficacy of cyclophosphamide. Isorel was found to increase the reactivity of tumor-bearing mice lymphocytes to the mitogens (ConA and LPS) in vitro, showing immune activating activities for the cancer-immunosuppressed lymphocytes [89]. A systematic review of 41 publications on the clinical effect of Iscador mistletoe extract usage on survival of cancer patients, showed better survival on adjuvant treatment with the Iscador extract [90].

10. Zingiberaceae Family: this consist of important plants like ginger, turmeric, cardamon and galangal which have wide ranges of medicinal values.

a) Ginger (Zingiber Officinale): a rhizomatous herbaceous perennial plant of the zingiber genus, native to south east Asia. It is one of the oldest known spices.

It contains several bioactive components like phenolic compounds, terpenes, polysaccharides, lipids, organic acids and raw fibers. It has various pharmacological activities like antioxidant, anti-inflammatory, antimicrobial, anticancer, antiobesity, antidiabetic, neuroprotectic, etc effects. Its medicinal values are due majorly to its phenolic constituents like gingerols and shogaols [91].

A systematic review and meta-analysis of the antidiabetic (FBS and HbA1c) of patients in 8 randomized trials involving a total of 454 type 2 diabetes patients administered ginger therapy (1600 – 4000mg daily) was carried out. Results showed no significant difference in FBS, but a significantly improved HbA1c from baseline to follow-up. This means that ginger can exert blood glucose control over a longer period of time in type 2 diabetics [92].

In a study, an aqueous extract of raw ginger (500mg/kg) was given intraperitoneally for 7 weeks to STZ induced diabetic rats. The dose significantly reduced serum glucose, cholesterol and triglyceride and urine protein levels [93]. In another study, the juice of Z. officinale (4mg/kg) was given orally for 6 weeks to STZ – induced diabetic rats. A special attention was paid to the role of serotonin (5-Hydroxytryptamine; 5-HT) receptors in control of blood glucose. In normoglycemic rats, 5-HT (mg/kg i.p.) caused hyperglycemia and hyperinsulinemia, which was significantly inhibited by the juice of Z. officinale [94]. STZ-induced diabetic rats had significant increase in FBS and decrease in serum insulin level, but treatment with Z. officinale significantly reduced the area under curve of glucose and increased the area

under curve of insulin in STZ-diabetic rats [94].

Gingerol a bioactive constituent of ginger has been shown to modulate several of the signaling pathways associated with cancer, like Nuclear Factors (NF-ϰB), STAT3 signal transducer and activator, Activator Protein-1 (AP-1), β-catenin, EGFR and VEGFR, mitogen-activated protein kinases (MAPK), and pro-inflammatory mediators (TNF-α and COX-2) [95]. Zerumbone another bioactive constituent and main component of Zingiber zerumbet rhizomes known for its wide-spectrum role in treating multitargeted diseases, has been shown to have immunomodulatory and anticancer properties [96]. Apoptotic and anticancer effects of methanolic extract of Zingiber officinale rhizome (ZOME) were investigated against human cervical (HeLa) and breast cancer (MDA-MB-231). Antioxidant effects were investigated using 1,1-diphenyl-2-picryl hydroxide (DPPH) scavenging assay, 2,2' -azinobis-3-ethylbenzothiozoline-6-sulfonic acid (ABTS) cation decolorization test. Results showed that ZOME inhibited proliferation and colony formation and exhibited apoptotic effects in HeLa and MDA-MB-231 cells in time and dose dependent way. ZOME equally showed significant antiradical effects against DPPH and ABTS [97].

The decreased cell viability and apoptotic effects of ginger against human colorectal cancer cells (HCT116, SW480 and LoVo cells) have been linked to ATF3 promoter activation and resultant increase of ATF3 expression via ERK1/2 activation in human colorectal cells [98].

b) Turmeric (Curcuma Longa): perennial rhizomatous plant of curcuma genus, native to south east Asia, used as culinary spice and traditional medicine.

Turmeric contains chemical complex, but curcuminoids and essential oils are the 2 main groups that exhibits bioactive effects. Curcumin, a lipophilic polyphenol extracted from the rhizomes of this plant, is the most predominant curcuminoid, and known to modulate various signal pathways linked to the etiology and pathogenesis of cancer, cardiovascular, autoimmune, type 2 diabetes and other metabolic diseases [99,100]. Curcumin has significant antioxidant, anticancer and anti-inflammatory properties, while other curcuminoids and essential oils demonstrated fewer bioactivities [99,100].

A systematic review of 16 studies on the antidiabetic effect of Curcuma longa or curcumin showed curcumin antidiabetic properties is linked to its ability to inhibit oxidative stress and inflammation. It was equally found to significantly decrease fasting blood glucose, glycated hemoglobin and BMI [101]. Nanocurcumin is linked with a significant decrease in triglycerides, VLDL-c, total cholesterol, LDL-c, HDL-c, serum C reactive protein and plasma malonaldehyde [101]. Turmeric supplementation as an adjuvant to type 2 diabetes metformin treatment enhances synergistic effects and significantly reduces FBS and HBA1c levels with reduced lipid peroxidation and enhanced total antioxidant status [102]. The antidiabetic and pharmacokinetic properties of two turmeric extracts viz bio-enhanced turmeric (BTE) 30mg/kg and 60mg/kg, and regular turmeric extract (RTE) 30mg/kg, were assessed on streptozotocin-nicotinamide induced type 2 diabetic rats, orally for 30days [103].

Results showed that turmeric extracts of treated group demonstrated significantly blood glucose reduction than diabetic control group. Turmeric extracts enhanced beta-cell function and increased insulin sensitivity. FBS, oral glucose tolerance (60min) and oral glucose tolerance (120min) were significantly ($p<0.05$) higher in RTE - 30mg/kg compared to the BTE – 30mg/kg treated groups. BTE – 30mg/kg had more pancreatic bioavailability than RTE – 30mg/kg treated group. BTE extract was found to be more effective antidiabetic agent than RTE [103].

Curcumin anticancer, antioxidant and anti-inflammatory effects are mediated through modulation of many cellular signaling pathways. Curcumin modulates various transcription factors, inflammatory cytokines, enzymes, kinases, growth factors, receptors and different proteins with affinity varying from pM to mM ranges. Curcumin equally synergizes chemotherapeutic agents and radiotherapy [104]. The cancer cellular pathways modulated by curcumin includes Wnt/β-catenin, PI3K/Akt, JAK/STAT, MAPK, p53 and NF – k B signal pathways [105]. Curcumin (diferuloylmethane) exerts direct anticancer effects by inhibiting proliferation of different tumor types. It initiates down-regulation of transcription factors NF-kB, AP – 1 and Egr – 1; downregulation of expression COX2, LOX, NOS, NMP-9, uPA, TNF, chemokines, cell surface adhesion molecules and cyclin D1; downregulation of growth factor receptors (EGFR and HER2) downregulation of oncogenic miRNAs and upregulation of tumor-suppressive miRNAs; and inhibit the activity of c-Jun N – terminal kinase, protein tyrosine kinase and protein serine/threonine kinases [105,106].

Studies show that curcumin has advantages over conventional anticancer drugs due to its broad anticancer effects and less adverse and toxic effects. Pre – treatment with curcumin followed by 5 – FU synergized and increased the susceptibility of colon cancer cells/xenograft to the 5 – FU cytotoxicity [107]. Different concentrations of turmeric extracts were found in a study to significantly inhibit the viability of OVCAR – 3 ovarian cancer cells [108].

11. Ginseng (Panax Ginseng, Panax Quinquefolius): is a perennial herb of the Panax genus and Araliaceae (ivy) family, native to far east Asia and America. It is one of the most investigated traditional medicine in the world, and is well known for its medicinal values for thousands of years.

Ginseng leaf-stem extract consist of bioactive ginsenosides, polysaccharides, triterpenoids, flavonoids, volatile oils, polyacetylenic alcohol, peptides, amino acids and fatty acids. This extract has more quantities of the same bioactive constituents than the root [109,110]. Ginseng has proven multiple pharmacological uses including anticancer, antidiabetic, antioxidant, antiobesity, anti-inflammatory, immunoregulatory, neuroregulatory, wound-healing and antiaging properties, and high safety use [109,110].

Ginsenosides, which are triterpene saponins are the major and the most studied bioactive components of ginseng, and has multiple arrays of pharmacological activities. The actual amount and type of ginsenosides present, differ in a given ginseng species. Also, ginsenosides have the capacity to undergo biotransformation to bioactive metabolites like compound K by gut bacteria after ingestion [111]. Ginsenosides have multiple diversities ranging from multiple dimensions, including chemical structure, tissue spatial distribution, time, and isomeride. Protopanaxadiol, protopanaxatriol and C17 side-chain varied (C17SCV) manners are the major types of ginsenosides. Only 16 ginsenosides are commonly found in all parts of a ginseng, and the component of ginsenosides differs significantly in the different parts. Protopanaxadiol-type ginsenoside is predominant in root, rhizome, leaf, stem and fruit, while malonyl – and C17SCV – type ginsenosides are predominant in flower and flower bud compared to other parts [112]. Comprehensive reviews of the antidiabetic properties of ginseng showed that it possesses glucose-lowering properties in several diabetic animals. It equally prevented development of diabetic complications.

The main antidiabetic component of ginseng is ginsenosides and polysaccharides. The antidiabetic effects of ginseng are exerted through regulation of many signal pathways including IRS1/PI3K/AKT, LKBI/AMPK/FoxO1. AGEs/RAGE, MAPK/ERK, NF-kB, PPARδ/STAT3, cAMP/PKA/CERB and HIF-1α/VEGF, etc [113,114]. A systematic review and meta-analysis of efficacy of ginseng (Panax) on human prediabetes and type 2 diabetes showed that ginseng supplementation significantly decreased serum concentrations of fasting plasma glucose, total cholesterol, IL-6, and HOMA-IR (Homeostatic model assessment for insulin resistance) values, and increased TNF-α values [115]. A randomized double-blind, placebo-controlled clinical trial for antidiabetic effects of hydrolyzed ginseng extract (HGE), results showed that after 8 weeks of HGE, fasting plasma glucose and postprandial glucose were significantly reduced in the HGE group compared to the placebo group [116].

The main mechanism of ginseng anticancer effect includes cell cycle arrest, apoptosis /paraptosis activation, autophagy, and angiogenesis inhibition. The protopanaxadiol class ginsenosides are more effective than the protopanaxatriol class. Sugar compounds in ginsenosides inversely affect their antiproliferative properties [117]. Ginsenosides also, combine synergistically with conventional chemotherapeutics to enhance antitumor effects [118,119]. Ginsenoside Rh2, one of the main bioactive ginsenoside from panax ginseng exhibit anti-metastasis, promotes differentiation and reverses multi-drug resistance effects in multiple cancer cells, and ameliorates the side effects of chemotherapy or radiotherapy [120]. Ginsenoside Rp 1 another bioactive component of ginseng inhibited breast cancer cell proliferation and equally inhibited both anchorage-dependent and independent breast cancer cell colony formation. Rp 1 reduced the stability of IGF-1R protein in breast cancer cells, and also inhibited IGF-1R/Akt pathways [121].

12. Mushrooms: fungi are a kingdom of mainly multicellular heterotrophic eukaryotes hundreds of million years old in our planet; with mushrooms, yeast and mold as examples. Mushrooms are large, diverse, fleshy, umbrella – shaped fruiting body of certain fungi with many genera (Agaricus, Psilocybe, Pluteus, Amanita) found in in different types of habitats all over the world. The name mushroom is used to describe edible species eg portobellos (Agaricus bisporus), shiitake (Lentinula edodes), morels (Morchella esculenta), while toadstool describes the poisonous ones eg death cap (Amanita phylloides), false parasol (Chlorophyllum molybdites), ivory funnel (Clitocybe dealbata). The constituents of Common mushrooms are 90% water, 3% proteins, 5% carbohydrates, 1% fats and 1% vitamins and minerals.

Bioactive constituents of mushrooms include amino acids, fatty acids (oleic, linoleic and linolenic acids), vitamins, sterols and essential minerals. The carbohydrates constituents include trehalose, the α1→ α1 dimer of D-glucose. Polysaccharides comprise chitin, the fungal fiber, which is a homopolymer of N-acetylglucosamine. Some toxic metals like arsenic, mercury, etc have been known to contaminate fungi collected from polluted soils [122]. Mushroom polysaccharides have antidiabetic, anti-obesity, anticancer, antioxidant and antibiotic bioactive effects [122,123].

Polysaccharides and protein complexes, dietary fibers, and other constituents extracted the fruiting bodies, cultured mycelium, or cultured broth of medicinal mushrooms exhibited antidiabetic effects through various mechanisms which include glucose absorption inhibition, beta-cell damage prevention, enhanced insulin release, improved antioxidant defense, inhibition of inflammation, regulation of carbohydrate metabolism pathways, regulation of insulin-dependent and insulin-independent signaling pathways [124].

The antidiabetic effects of 8 mushroom species from China were investigated by in vitro α-glucosidase and aldose reductase (AR) inhibitory assays and antioxidant assay. The antioxidant effects of the selected mushrooms were investigated based on the total phenol content, flavonoids content and DPPH free radical scavenging effects. Results showed the mushroom species demonstrated varying degrees of potency with respect to their antidiabetic and antioxidant properties based on their total phenol and total flavonoids contents [125].

250, 500 and 750 mg/kg body weight of button mushroom (Agaricus bisporus) extracts were given orally to alloxan induced diabetic rats for 14 days. Results showed the extracts significantly reduced blood glucose, malondialdehyde (MDA), and increased superoxide dismutase (SOD) activity. The secondary metabolites of A. bisporus determined by thin layer chromatography are flavonoids, alkaloids, terpenoids, and saponins [126]. 200 and 400mg/kg body weight of hot water extract of polysaccharide from Hypsizygus ulmarius (HUP) mushroom were supplemented in STZ-Nicotinamide induced diabetic rats. Results showed that HUP inhibited α-amylase and α-glucosidase enzymes, with reduction in FBS, serum lipid metabolism, lipid peroxidation and increase in insulin levels and antioxidant enzyme activities, comparable to that of glibenclamide a conventional antidiabetic

which was the positive control [127].

Mushrooms and their extract have immunomodulatory and anticancer activities. The major bioactive constituents of mushrooms responsible for their anticancer effects are 1) polysaccharides like β-D glucan (trade names D and MD fractions, Lentinan, Schizophyllan) and polysaccharide-protein complex like PSP, PSK (Krestin). Carboxymethylated, hydroxylated, formylmethylated, aminethylated and sulfated products of these polysaccharides have been designed to improve their anticancer effects [128]. 2) Proteins like lectin and laccase, hemolysin, ribonucleases, ubiquitin conjugated proteins and lentin. 3) Cytotoxic terpenoids, steroids, phenols, and dietary fibers [128].

The methods of extracting these bioactive constituents from mushrooms include ethanol, methanol, ethyl acetate, hot water, acetone, ether-ethanol, ethanol-ethyl acetate-chloroform extracts. The novel approaches of cancer treatment with mushroom products include Vaccinotherapy and Nanovectors drug delivery [128]. Mushroom derived polysaccharides showed significant anticancer effects against various metastatic cells and better effects in conjunction with chemotherapy. The anticancer effects are mediated via thymus-dependent immune systems, which require intact T cell. Bioactive Polysaccharides activate cytotoxic macrophages, NK cells, dendritic cells, monocytes, neutrophils and chemical messengers that activates complementary and acute responses. Polysaccharides act as multi-cytokines activators, inducing gene expression of many immunomodulating cytokines and their receptors [129]. Terpenes activate the expression of genes coding for proteins involved in immune response. Lectins have anticancer and antiproliferating activities. Phenolic compounds are well known antioxidants [129].

A systemic review and Random meta-analysis of 17 journal on link between mushroom intake and risk of cancer published between 1 January, 1966 to 31st October, 2020 was carried out. Results revealed that greater consumption of mushroom was associated with lower risk of total cancer. There was a significant nonlinear dose-response link between consumption of mushroom and lower risk of breast cancer [130]. Various mushroom species have been investigated for phase I and II clinical trials. The percentages of anticancer clinical investigations involving mushroom include breast cancer (18.6%), colorectal cancer (14%), and prostate cancer (11.6%). Predominant clinical investigations were carried out with Lentinula edodes (22.2%), Coriolus versicolor (13.9% and Ganoderma lucidum (13.9%), Agaricus bisporus (11.1%) and Grifola frondose (11.1%) [129].

A pooled analysis of Miyagi and Ohsaki cohort studies on mushroom consumption and incidence of risk of prostate cancer, involving a total of 36, 499 men aged 40 – 79 years, showed that the rate of mushroom intake was linked to reduction in risk of prostate cancer. The inverse association was more prominent in men ≥ 50 years and was not affected by the clinical stage of cancer, or intake of vegetables, fruits, meat and dairy products [131].

Table 1: Showing Summary of Antidiabetic-Anticancer Dual-Active Plants.

SN	PLANTS	PHYTOCHEMICAL CONTENTS	MECHANISM OF ACTION AND ROLES.
1	Garden Egg (Solanum melongena)	Solasonine, Solasodine, Solamargine.	Antioxidant, α-amylase, α-glucosidase inhibition, cytotoxic, antiproliferation.
2	Tomato (Solanum lycopersicum)	Tomatine, Lycopene, Kaempferol.	Antioxidant, HbA1c and lipid peroxidase reduction, Anticancer.
3	Irish potato (Solanum tuberosum)	phenolic acids, anthocyanin, flavonoids, vitamin B6, B3, pantothenic acid	Anti-obesity, Antidiabetic, Apoptotic, AKT/ mTOR,regulation
4	Bitter leaf (Vernonia amygdalina)	Vernodalin, Vernomygdin, Vernoniosides (A1, A2, A3, A4, B1, B2, B3, D and E), Vernodalol and Epivernodalol [17] [21]. acidic lipid, mucilage, pectin, lipids, polyphenols and alkaloids. glucosides, diterpene, lactones, andrographolide, flavonoids.	Antioxidant, Decreased expression of gluconeogenesis enzymes and increased expression of G6PHD enzymes. Metabolic enzyme inhibition, Pancreatic β-cell regeneration. Apoptotic, Decrease cell viability, DNA synthesis inhibition, DNA Damage.
5	Neem (Azadirachta indica)	nimbin, nimbidin, nimbolide and limonoids. Polyphenolic flavonoids quercetin and β – sitosterol	Blood glucose, Serum insulin. Lipid profile and insulin signaling molecules, as well as GLUT 4 proteins regulation. Antitumor, Antioxidant and Apoptotic, Oncostatic,
6	Citrus Genus	vitamin C and phytochemicals (carotenoids, polyphenols, phenolic acids, flavonoids, coumarin, terpenoids, saponin, stilbenes, lignans etc)	Antioxidant, Antihyperlipidemic, Cardioprotective. Antiproliferation, Antiangiogenesis, Anti -metastatic, Anti- inflammatory and Apoptotic

7	Sweet wormwood (Artemisia annua)	Dicaffeoylquinic acids, Chrysosplenol D, Arteannuin B, Casticin. Arginine, Chlorogenic acid, Caffeoylquinic acids, Saponins, Thujone and Pentacyclic triterpenes, Arachidonic acid.	Antioxidant, inhibition of dipeptidyl peptidase IV, α – glucosidase, α – amylase and aldose reductase enzymes. Transdifferentiation of α- to β-cell. Accumulation of multinucleated cancer cells within 24 hr of treatment, increase in the number of cells in S and G2/M phase of cell cycle and activated caspase 3.
8	Aloe Vera (Aloe barbadensis, Aloe indica, Aloe africana)	Anthraquinones, Aloin, Emodin, Alomicin, Aloe mannan, Aloesin. vitamins (A, C, E and B12), enzymes (Amylase, catalase, peroxidase), minerals (zinc, copper, selenium, calcium), sugars (monosaccharides and polysaccharides), fatty acids (lupeol and campesterol), hormones (auxins and gibberellins), and others (salicylic acid, lignin and saponin)	Anti-obesity, α-amylase and β-glucosidase inhibition. Cytotoxic, Anthraquinone Derivative block phosphorylation of Her2/neu, suppress growth, transformation and metastasis as well as tyrosine kinase inhibitor.
9	Grapes (Vitis vinifera)	Hydroxycinnamic acids, Stilbenes (resveratrol), Flavonoids (including anthocyanins, proanthocyanidins, quercetin), Phytosterols and Fatty acids. gallic acid, cyanidin-3-glucoside, epicatechin, catechin gallate, ferulaic acid, rutin and resveratrol.	Antioxidant, Antihyperglycemia, decrease the lipid peroxides and carbonylated proteins. Cytotoxic, antiproliferation.
10	Garlic and Onion. (Allium genus)	Allicin, S-methylcysteine sulfoxide, S-allylcysteine sulfoxide and diallyl trisulfide.	Antioxidant, increased fasting serum HDL levels with hypoglycemic and hypolipidemic effects. Regulation of liver glucose activities. Anticancer, decrease cancer risk.
11	Mistletoe (Viscum album)	Lecithins (ML I, II, III), viscotoxins, kuttan's peptides, oligo- and polysaccharides, lipids, flavonoids, thiols, plant acids, phytosterols and sterols, phenylpropanes, lignans, alkaloids, minerals, trace elements, proteins, triterpenes.	Insulin-releasing, Antidiabetic. Cytotoxic, Adjuvant chemotherapeutic.
12	Turmeric (Curcuma longa)	Contains chemical complex, but curcuminoids, Curcumin and essential oils are the main bioactive constituents.	Decrease in blood glucose, glycated hemoglobin, BMI, triglycerides, VLDL-c, total cholesterol, LDL-c, HDL-c, serum C reactive protein and plasma malonaldehyde. Modulates various transcription factors, inflammatory cytokines, enzymes, kinases, growth factors, receptors and different proteins
13	Ginseng (Panax ginseng)	Ginsenosides, polysaccharides, triterpenoids, flavonoids, volatile oils, polyacetylenic alcohol, peptides, amino acids and fatty acids.	Regulation of IRS1/PI3K/AKT, LKBI/AMPK/FoxO1. AGEs/RAGE, MAPK/ERK, NF-kB, PPARδ/STAT3, cAMP/PKA/CERB and HIF-1α/VEGF. Cytotoxic, reverses multidrug resistance.
14		Amino acids, fatty acids (oleic, linoleic and linolenic acids), vitamins, sterols and essential minerals. Trehalose, chitin, fungal fiber, which is a homopolymer of N-acetylglucosamine.	Glucose absorption inhibition, beta-cell damage prevention, enhanced insulin release, improved antioxidant defense, inhibition of inflammation. Thymus-dependent immune systems, activation of cytotoxic macrophages, NK cells, dendritic cells, monocytes, neutrophils.

1. 2 Other Bifunctional Plants with Reported Dual Antidiabetic-Anticancer Effects

Many other plants and plant product have demonstrated varying dual antidiabetic – anticancer effects. Potential to proven potent bifunctional antidiabetic – anticancer plants include:

1. Noni (Morinda Citrifolia): evergreen poly-nutrient superfood plant native to south east Asia and Australia, used in traditional medicine for treatment of wide ranges of diseases and illness.

It's very rich bioactive constituents include iridoid glucosidases, 6α-hydfoxyadoxoside (1) and 6β,7β—epoxy-8-epi-splenoside (2), and also 17 other known components like americanin A (3), narcissoside (4), asperuloside, asperulosidic acid, borreriagenin, citrifolinin B epimer a, citrifolin B epimer b, cytidine, deacetylasperuloside, dehydromethoxygaertneroside, epi-dihydrocomin, d-glucose, d-mannitol, methyl α -d-fructofuranoside, methyl β-d-fructofuranoside, nicotifloroside, and β-sitosterol 3-O-β-d-glucopyranoside [132].

Morinda citrifolia has potent antidiabetic and anticancer properties [133-137].

2. Prekese (Tetrapleura Tetraptera): a flowering plant in the pea family native to West Africa, where it has cultural importance in the preparation of spicy meals for postpartum care and also in traditional medicine. It is widely known for its various anticancer, antidiabetic, antioxidant, anti-inflammatory, antimicrobial etc. medicinal properties.

Its bioactive constituents include polyphenol, flavonoids, saponin, tannin and phytates. Also, sugar, starch, crude proteins, Zn, Cu, Mg, Mn, Na, Ca and K, whose concentration and composition differ in different parts of the plant [138]. Tetrapleura tetraptera has proven antioxidant, antidiabetic and anticancer effects [139-142].

3. Berry Family: commonly (but not scientific nor botanical) used to refer to small, pulpy, edible and juicy fruits without stone or pit native to Europe. Examples include cranberry, blueberry, strawberry, Huckleberry, chokeberry, raspberry, blackberry, elderberry, gooseberry, raspberry, Acai berry, goji berry, mulberry, lingonberry, olallieberry, boysenberry, red currant, white currant, blackcurrant, pomegranate etc.

The bioactive constituents of berry include mainly phenolic compounds (phenolic acids, flavonoids, such as anthocyanins, flavonols and tanins) and ascorbic acids [143] that possess powerful antioxidant effects due to their free radical scavenging and DNA damage protection [143,144].

Berries are known for their potent antidiabetic and anticancer properties [145-148].

4. Burdock (Actium Lappa): a fibre-rich vegetable native to Japan whose root has been used for medicinal values for centuries.

Burdock root has been reported for treating chronic illness like cancer, diabetes and AIDS [149].

The main bioactive constituents of burdock include caffeoylquinic acid derivatives, lignans (mainly arctiin), and flavonoids. The bioactive compounds in: a) burdock seeds are phenolic acids (caffeic acid, chlorogenic acid and cynarin), b) burdock roots are arctiin, luteolin and quercetin rhamnoside, c) burdock leaves are phenolic acids, quercetin, quercitrin and luteolin [150].

Burdock has documented antidiabetic and anticancer properties [151-156].

5. Beetroot (Beta Vulgaris): is the taproot part of the beet plant. It is nutrient and fiber rich and important source of nitrates.

Beetroot has multiple bioactive phenolic compounds made up mainly of betalins and other constituents with antioxidant effects like coumarins, carotenoids, sesquiterpenoids, triterpenes and flavonoids (astragalin, tiliroside, rhamnocitrin, kaempferol, rhamnetin) [157]. Beetroot is stable, nontoxic, non-carcinogenic and nonpoisonous [158].

Beetroot has known antidiabetic and anticancer activities [159-163].

6. Cucumber or Gourd Family: This is a large family of varieties of plants including cucumber (Cucumis sativus), different melons including watermelons, bitter melon (Momordica charantia), gourds, squash, pumpkin, zucchini etc.

Cucumber (Cucumis Sativus) has known antioxidant and antidiabetic activities. The bioactive components include cucurbitacins, cucumegastigmanes I and II, cucumerin A and B, vitex, orientin, Isoscoparin, glucoside, apigenin etc [164]. Curcubitacin bioactive constituent has potential anticancer effects [165].

Bitter Melon (Momordica Charantia) contains triterpenoids, saponins, polypeptides, polysaccharides, flavonoids, alkaloids and sterols and has potent antidiabetic and anticancer effects [166-170].

7. Cinnamon (Cinnamomum Verum, Cinnamomum Zeylanicum): a popular spice gotten from the bark of cinnamon tree; fibre and nutrient rich and used for flavoring.

Cinnamon mainly contains important oils and other extracts like cinnamaldehyde, cinnamic acid, and cinnamate [171]. It has proven antidiabetic and anticancer properties [172-174].

8. Soursop or Graviola (Annona Muricata): is tropical fruit that is grows on Annona muricata tree and is native to America. It is a superfruit with high nutrient profile and potent antioxidant with important traditional medicine application.

Extracts from the fruit, bark, seeds, roots and leaves of graviola contain dozens of acetogenins, a class of bioactive polyketide-derived components [175].

Annona muricata has proven potent antioxidant, antidiabetic and

anticancer effects [176-179].

9. Carrot (Daucus Carota): Is a root vegetable with high nutrient and antioxidant profile, and claim to be the perfect health food. It especially rich in beta carotene an antioxidant which the body converts to vitamin A.

The 4 types of phytochemicals found in carrots are phenolics, carotenoids, polyacetylenes and ascorbic acid. High contents of α and β- carotene are found in orange carrots (which gives them bright orange color), lutein in yellow carrots, lycopene in red carrots, anthocyanins in the roots of purple carrots, and phenolic compounds in black carrots [180].

Carrot has notable antioxidant, antidiabetic and anticancer effects that has been reported [181-184]

10. Myrtaceae Family: this family includes clove (Syzygium aromaticum), guava (Psidium guajava), eucalyptus (Eucalyptus globus), Gabiroba (Campomanesia xanthocarpa).

a) Clove (Syzygium Aromaticum): a tropical evergreen plant of the family Myrtaceae native to Indonesia, used for flavoring food products or as fragrance in toothpaste, soap or cosmetics.

Clove has potent antidiabetic and anticancer potentials [185-189].

b) Eucalyptus (Eucalyptus Globus): fast – growing evergreen shrubs and trees native to Australia, popular used in the management of various respiratory illness. Eucalyptus oil is a 'do – it – all' essential oil. It is a common ingredient of decongestants, cough and cold medicines.
Eucalyptus has reported antidiabetic and anticancer activities [190-194].

11. Red Clover (Trifolium Pratense): is a short – lived perennial flowering plant eaten as legume and used in traditional medicine to treat various diseases especially menopause (and its symptoms), cancer and inflammation.
Red clover has known antidiabetic and anticancer effects [195-199].

12. Asparagus (Asparagus Officinalis): is a perennial flowering plant in the genus Asparagus native to western Asia, North Africa and Europe, and used as food and medicine as far as 3, 000 BC.

Asparagus has proven potent antidiabetic and anticancer properties [200-205].

1. 3 Other Bifunctional Common Fruits and Vegetables with Potential Dual Antidiabetic-Anticancer Effects.

Common fruits and vegetables with potential dual antidiabetic and anticancer effects that need to be explored are listed below.

1. Cashew (Anacardium occidentale)
2. Mango (Mangifera indica)
3. Guava (Psidium guajava)
4. Okra (Abelmoschus esculentus)
5. Pawpaw (Carica papaya, Asimina triloba)
6. English pear (Pyrus communis)
7. Avocado pear (Persea americana)
8. Maize (Zea mays)
9. Sorghum (Sorghum bicolor)
10. Apple (Malus domestica)
11. Cherry (Prunus avium)
12. Tea (Green tea, Black tea, Hibiscus tea, Chamomile tea)
13. Nuts (Almond, Walnut, Chestnut, Peanut, Hazelnut, Tigernut)
14. Spinach
15. Cruciferous vegetable (Broccoli, Broccoli sprouts, Brussels sprouts, Cauliflower, Radish, Bok Choy, Garden Cress, Mustard plant, Kale, Collard green, Arugula and Cabbage)

Bifunctional Plants with Dual Antidiabetic – Anticancer Effects: New Roles and Prospects

Challenges in the Use of Bifunctional Dual-Active Antidiabetic-Anticancer Plants as Pharmaceuticals:
Although, these bifunctional dual-active antidiabetic-anticancer plants offer cheap, reliable and accessible opportunities compared to conventional drugs, with reported proven effectiveness in the management of both diabetes and cancer, these opportunities have not been fully utilized due to a number of factors.
These challenges include 1) the huge cost and developmental processes involved in new drug development may present a giant barrier in turning these promising opportunities into reality for pharmaceutical companies, especially in developing countries, unless they are very sure that the risk is worth taking. Hence, effective encouragement and collaboration between the Government and these companies are required in this regard. 2) procurement of some of these plants in sufficient quantities in other to make the commercialization of their products economically viable for pharmaceutical companies especially in chronic diseases like diabetes and cancer, and this may require extensive cash cropping of these plants. 3) techniques and methods for successful extraction, isolation and assaying of the bioactive products, as these plants are known to contain so many other unrelated and inactive constituents which may in some cases occur naturally as complexes with the main active constituents. 4) Chemotherapeutic drugs require high level of quality assurance and regulation in their manufacturing process and these may be lacking in some cases leading to substandard, fake products and unacceptable number of recalls from market.

5) after isolation, these bioactive constituents have to undergo several steps of preclinical and clinical trials to establish their dose, efficacy, tolerability, safety and toxic profiles after which they are assessed for economic and commercial viability. The toxic profiles of many of these plants are not known ab initio and these present usage challenges. 6) some of these plants after satisfactory safety profiles have been established, do not have appreciable bioavailability through their effective routes of administration, and may require the use of drug delivery systems

to obviate this challenge.

That notwithstanding, there are increasing interests in the use of plants and plant products as natural remedies for chronic illness due to renewed interests from pharmaceutical companies, newer innovations and scientific pursuits, newer advances in fractionation and extraction technologies of bioactive products and newer manufacturing processes which are addressing these challenges.

Bifunctional Dual- Active Antidiabetic-Anticancer Plants Prospects: The use of these bifunctional dual-active antidiabetic-anticancer plants should be extensively researched and exploited for the advantages they offer. Many of these plants have been used for thousands of years in folk and traditional medicine settings and they are still as effective as ever.

The list of these plants is inexhaustible, and they should be identified, assessed and extensive preclinical and clinical trials carried out to ascertain their level of efficacies and effectiveness in the management of diabetic patients with concurrent cancer illness and cancer patients with glucose intolerance.

These plants and their products should be studied to ascertain their best and most effective regimen viz. monotherapy, combination therapy with conventional drugs, adjuncts, alternatives, first- or second-line therapies etc.

The various plants extracts and bioactive constituents cand equally be combined to enhance their potencies as several of them act through various and different pathways to exert their antidiabetic and anticancer effects. For example, the combined extracts and bioactive constituents from the Allium and Berry families of plants can be studied for their antidiabetic-anticancer effects.

Complexes, ions, ionophores and various drug delivery systems can be used to increase the bioavailability and pharmacological efficacies of these antidiabetic-anticancer bioactive plants.

2. Conclusion

The pharmacological effectiveness of plants has been known to man for thousands of years, where they have found use in folk medicine in the management of many diseases and ailments due to their multiple pharmacological properties.

This article reviewed common and known plants with dual-effective antidiabetic-anticancer properties, their bioactive constituents, various pharmacological effects, their challenges and prospects.

It is hoped that key pharmaceutical agents with dual antidiabetic-anticancer effects will be developed from the bioactive constituents of these plants or their combinations as monotherapies, combination regimens, adjuncts, or alternatives to conventional drugs.

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