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Bioactivity and Therapeutic Potential of Plant Extracts in Cancer and Infectious Diseases

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Abstract: Medicinal plants have been used particularly in resource poor communities of the African continent as an alternative for the treatment of infectious diseases. Traditional medicine plays a critical role in treatment of chronic debilitating and life threatening conditions and infectious diseases. Cancer is one such condition whose therapeutic intervention is commonly through inexpensive traditional herbal remedies. Increasingly industrialised societies are developing drugs and chemotherapeutics from these traditional herbal plants. Plant biogeography determines the abundance and availability of medicinal plants which in turn determine their use by africango communities. Recent findings of bioactivity and therapeutic potential of plant extracts in cancer and infectious diseases are herein summarized and discussed.

Keywords: Antioxidants, Chemotherapy, Medicinal Plants, Phytochemicals, Prophylaxis, Herbs, Natural Products, Cancer, Infectious Diseases

1. Introduction

Medicinal plants have been used particularly in resource poor communities of the African continent as an alternative for the treatment of infectious diseases [1], cancer [2] and other deseases [1,2]. Several findings on the chemotherapeutic potentials of plants have shown that they can be sources of antimicrobial compounds of valué [3]. A typical example of such plants is *Garcinia kola.*

They contain large varieties of chemical substances that possess important therapeutic properties used in the treatment of many deseases. Plant extracts are rich source of terpenes, antioxidant phenolics, flavonoids and other biologically-active compounds. In modern medicine these compounds have been investigated for their anthelmintic and antioxidant activities in parasitized animals by neutralizing the free radicals and toxins formed in their blood, boost their immune system, and help fighting gastrointestinal parasites [4].

Natural bioactive compounds like phenols and flavonoids are the important secondary metabolites in plants having intrinsic properties that affect appearance, taste, odor and oxidative stability of plant based foods. These compounds also posses biological properties like antioxidant, anti-aging, anti-carcinogen, protection from cardiovascular, immune/autoimmune diseases and brain dysfunctions viz. Parkinson's, Alzheimer's, Huntington's diseases, etc [5,6]. Therapeutic potential of A. absinthium extract is directly related to total phenolic and flavonoids contents. These active metabolites especially from herbs are the interest subject of research, but their extraction as part of phytochemical or biological investigations presents specific challenges that must be addressed throughout the solvent extraction process. The present review summarizes and discusses the current understanding of bioactivity and therapeutic potential of plant extracts in cancer and infectious diseases.

2. Cancer and Infectious Diseases is There any Link Between Cancer and Infectious Diseases

Infection is considered as a major risk to develop cancer, among all newly cancer diagnosed in 2008, almost 16% were attributed to infection agents[7]. This percentage is most high in developing countries, probably due to the fact that they have a high incidence of infectious disease [8, 9]. Many infections agents including viruses, parasites and bacteria are classified as group 1 carcinogenic agents by the International Agency for Research on Cancer (IARC). Epidemiological evidences and molecular mechanisms bridge a correlation between infections and cancer. For example, human cytomegalovirus (HCMV) is found in high percentage of glioblastoma patients, and the association of anti cancer therapy to antiviral therapy against HCMV increases median survival of patient with glioblastoma multiforme [10, 11]. In fact there are 7 mains infectious agents for whom there are enough of evidences to be classified as human carcinogens: hepatitis B virus (HBV), hepatitis C virus (HCV), certain strains of the human Papilloma virus (HPV), Helicobacter pylori (H. pylori), Epstein-Barr virus (EBV), human immunodeficiency virus type 1 (HIV1), and human T-cell lymphotropic virus type I (HTLV1) and the Kaposi's sarcoma herpesvirus (KSHV) [12]. Except these well known agents there are others whose infection is associated to the development of the oncogenic process. In the study of Samaras et al. [13], they queered on many data bases articles based on a correlation between cancer and parasite/bacterial infections. They found for some agents including salmonella tiphy (S. Tiphy), Opisthorchis viverrini, Clonorchis sinensis and Schistosoma hematobium, high evidence of association between infection and cancer. It's noteworthy to highlight again that these infections are more frequent in developing countries. The association between infection and oncogenic process has two great implications: First, cancer appears in this point of view as potential transmitted disease. Secondly, known that there are efficient therapies or vaccines available for infectious diseases, cancer could then be prevented. For instance H. pylori infection is associated with a risk to develop gastric cancer. So, early eradication of this bacterium is associated with the decrease risk of gastric cancer in patient with gastric cancer [14]. Similarly vaccination against HPV, and HBV are respectively used to fight cervical cancer and hepatocelular carcinoma [15,16]. However the understanding of mechanisms paving the ways from infection to cancer remains to be clarified. Some oncogenic pathogens directly transform cell into tumour cells while others create an inflammatory and oxidative environment, promoting cancer development. These mechanisms include perversion of genome stability and cell cycle regulation, perturbation of the balance between oncogenes and tumour suppressors, creation of chronic inflammatory and oxidative environment. As result of these conditions created by infectious agent, resident cells will undergo mutations, cell proliferation, resistance to cell death and angiogenesis.

2.1. Genome Instability

Many infectious agents in the course of the infection will affect the genome either by subverting host replication for their own replicative process, or by secreting substances able to affects genome integrity. Among all infectious agents, viruses have the first place as agents causing genome instability. Consistent with this the study of virus biology has been helpfull for the understanding of genome. When the virus is inside the host cells, the viral particle which is basicaly a molecule of DNA or RNA, could be integrate in host chrosmosome, in order to replicate viral particle and direct the expression of genes necessary for the formation of new viral particle. This integration is cause of insertion mutation including DNA rearrangement such as translocation, deletion, sequence duplication as well as, viral promoter-driven human transcription, viral-human transcript fusion, and DNA copy number alteration associated to cancer development [17]. The study of Paterlini-Bréchot et al [18], consistent with many other studies, highlights the high prevalence in human liver cancers of HBV-DNA integration in genes involved in cell signalling. In patients suffering from cervical cancer, Campitelli et al [19] report that mutational insertion constitutes a highly specific molecular marker of circulating tumor DNA in HPV-associated tumor patients. However All the microbse are not able to integrate host genome to induce genome instability, some could secrete genotoxic compounds able to directly induce DNA lesions or which can target protein responsible of the control of genome integrity. The bacterium S. tiphy is the cause of typhoid fever which is very frequent in developing countries. Chronic S. tiphy infection seems to be an important risk to develop carcinoma of gallbladder [20]. However except the metabolization of bile salt into carcinogenic compounds [21], S. tiphy produces also genotoxic coumpounds including cytolethal distending toxin B (CdtB) [22]. CdtB is a subunit of the virulence factor CDT producing by many bacteria. Once in the host cell, Cdt goes to the nucleus and breaks double-stranded DNA, resulting in the arrest of the cell cycle at the G2/M boundary [23].

2.2. Target of Cellular Oncogene or Tumor Suppressor by Infectious Protein

Infectious agents can produce proteins capable to affect the balance between tumour suppressor and oncogene. The infectious protein can achieve these actions by activating oncogene, while deactivating tumour suppressor or simply acting as normal cellular oncogene, thereby contributing to the oncogenic process. HPV infection illustrates clearly this, in fact the oncoproteins E7 and E5 of the human papilloma virus 16 bind and functionally inactivate tumor suppressor proteins p53 and Rb, respectively, and both disrupt the G1 arrest in response to DNA damages [24]. Viral or bacterial protein could be homologue of cellular protooncogene, or activate a cellular proto-oncogene. So the protein BHRF1 of

EBV virus is a homolog of the cellular ant apoptotic Bcl-2 protein. Expression of BHRF1in human B cells protects them from programmed cell death like the cellular Bcl-2 [25]. The Virulence factor cytotoxin associated gene A of H. Pylori (CagA), is known to be critical to many H. Pylori outcomes including gastric carcinoma. Cag A is directly injected in host cell by the bacterium, and once in the host cell can specifically and physicaly bind to many cellular protein and modify their activity. For instance the Src homology 2 (SH2) domain containing phosphotyrosine phosphatase 2 (SHP-2) is the product of cellular oncogene PTPN11. Dysregulation or simply activation of SHP-2 is involved or found in the development of many malignancies including leukaemia and solid tumors [26]. CagA binds in phosphorylation-dependent manner to SHP-2 and thereby stimulates the phosphatase activity of SHP2 [27].

2.3. Infection and Inflammation Mediated Cancer

The infection mediated carcinogenesis, presented above relies on the ability of infectious agents or particles to inter into the host cells, however many microbes known as potential inducer of cancer are not able to inter into the host cell neither to produce protein able to do that. They act by changing the cell environment. In fact one major mechanism of carcinogenesis is chronic inflammation, it's known as the 7th hallmark or cancer development [28]. Therefore, inflammation induced by infectious agent is one main mechanism of infection related cancer. For instance shistosomiasis induces chronic inflammation of the bladder, which seems to be associated with initiation of bladder cancer [29]. The presence of infectious agents in the body will trigger inner and acquired immunity, both associated with inflammatory response. The persistence of the infectious agent will then create a state of chronic inflammation. Generally infectious site is characterized by infiltrating immune cells; they will then produce pro-inflammatory cytokine, growth factors, and will release active oxygen species. Active oxygen species are most responsible of DNA damage and thus promote the initiation of the tumour [30]. Inflammatory cytokines, will stimulate proliferation, escape to cell death, angiogenesis and acquisition of invasive phenotype. An illustration of this is H. Pylori infection, which induces chronic gastric inflammation, which is a home to cancer. In fact Helicobacter gastritis compared to others gastritis is characterized by high infiltration of mucosal levels of inflammatory cytokine, including IL-1β, IL-6, IL-7, IL-8, IL-10 and TNF-α [31]. These cytokines are able then to modulate cell necrosis [32], affect the stability of the genome and modulate gene expression, cell growth and resistance to cell death. Accordingly, the chronic inflammatory response in HBV infected liver, gives rise to cirrhosis and hepatocarcinoma. In the study of Yu and colleague, IL-29, IL-8, and cyclooxygenase-2 were shown to be highly expressed in HBV infected patient or in HBV expressing cells [33]. Another mechanism featuring immune response related inflammation is the activation of the inflammasome. This response is activated when the cytosolic nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) recognize PAMPs in intracellular compartments. Inflammasome response consist in activation of caspase1 by a platform of proteins, this caspase 1 will then induces the maturation of cytokines, including IL-1β and IL-18 [34]. Inflammasome activation is undergoing by hepatic Macrophages following HCV infection, resulting in production of IL-1β, whose action leads to liver inflammation [35]. Il-1β, IL-18 and caspase 1 is found in the inflammatory environement associated to KSHV infection. During KSHV infection of endothelial cells, interferon gamma-inducible protein 16 (IFI16) interacts with the adaptor molecule ASC and procaspase-1 to form a functional inflammasome, which is responsible of the maturation and production of IL-1β and IL-18. This could be a potential mechanism of inflammation associated lesion found in Kaposi's sarcoma [36, 37]. There are some evidences of possible association between Mycoplasma hyorhinis (M. hyorhinis) and the development of gastric and prostate cancers [38, 39]. Macrophages challenged with M.hyorrhinis, underwent inflammasome activation and production of IL-1β capable to promote gastric cancer cell migration and invasion [40]. The Inflammatory process required implementation of specifics intracellular mediators, including NF-κβ, Stat3, and mitogen-activated protein kinases JNK and P38. These proteins are cruxial for the tumor development, regulating proliferation, cell death, migration angiogenesis and invasion. The detailed mechanism related to each of this protein is over the scope of this review, so we will focused only on NF-κB and Stat3 for their highly importance in inflammation related cancer. In fact their role in infection related inflammation and cancer is well documented, and they seem to be involved in major cases of infection induced inflammation related cancer, moreover, there are established synergistic crosstalk between the NF-κB signalling and the Stat3 signalling in tumors [41-46].

Proteins NF-κB is a family of transcription factors commomly expressed in almost all cell types and involved in immune response. NF-κB signalling, is found in the cytoplasm sequestered by proteins IKb, cytokine signalling will induce the degradation of IKb in IKKB dependent way. Proteins NF-κB will then go into nucleus and trigger transactivation of many genes encoding for proteins regulating inflammation cell growth, cell proliferation, cell death, motility and angiogenesis [47-48]. NF-κB is overexpressed in many cancers, and has a pivotal role linking inflammation to cancer [49]. Many observations illustrate the major and ubiquitous role of the protein NF-κB in infection related cancer: H. Pylori infection on gastric epithelial cells induces NF-κB activation [50]. NF-κB is constituvely activated in Primary effusion lymphomas (PELs) associated with infection by KSHV [51]. The EBV latent membrane protein 1 (LMP1) is known to be sufficient to immortalize B cells. Expression of LMP1 in B cells induces NF-κB activation and stimulates proliferation of these B cells. HTLV-I infection is causally associated with a variety of human diseases including leukemia/lymphoma. HTLV-I

triggers a persistent activation of NF-KB, modifying the expression of a large array of host genes, participates as such to the initiation of T-cell transformation. The Tax protein encoded by HTLV-1 is an oncoprotein capable to immortalize human T cell and induces tumor in animal models [52, 53]. Tax is known to induce constitutive nuclear expression of NF-κB, causing aberrant expression of cellular genes associated to the tumorigenesis [54, 55].

stat3 is a major mediator of the inflammatory response, its favours tumour cell proliferation, survival angiogenesis and suppress anti-tumour immunity [45, 46]. Activation of STAT3 occurs in many infection-related cancer including HPV-related cervical cancer, HCV and HBV-related hepatocarcinoma, Kaposi's Sarcoma [56-59]. For instance, In HPV-16 positive cervical cancer cell, Shukla et al.[56] found a correlation of constitutive active STAT3 with expression of HPV16 E6 and E7 oncoproteins and a negative association with levels of p53 and pRB. Activation of STAT3 is very rapid during the infection and is triggering by many cytokines and growth factors. For example following the infection of S. typhi, activation of STAT3 is observed in macrophages at 6h post infection [60]. Punjabi and co-worker [58], observed by infecting endothelial cells with KSHV a phosphorylation/activation of STAT3, and this activation persists as long as latent infection is maintained, giving as such the evidence that KSHV induced activation of STAT3 could be critical for pathogenesis of Kaposi's sarcoma. More insight were gaining by the work of Christine King [61], showing that activation of KSHV-induced activation of Stat3 required the phosphorylation/activation of STAT3 coupled with inactivation of TRIMP28, a negative regulator of STAT3.

3. Plant Extracts as Therapeutic Potential in Infectious Diseases

The discovery of antibiotics has decreased the spread and severity of a wide variety of inferior diseases. However, and as a result of their uncontrolled use, the efficiency of many antibiotics is being threatened by the emergence of microbial resistance to existing chemotherapeutic agents [62]. While bioactive natural compounds have been isolated mainly from cultivable microbial strains, an untapped biologically active metabolites of different resources including plants remains to be investigated [63] to alleviate or help responding to current health care situations; such situations include but not limited to unmet clinical needs, increasing cost of chemotherapy, mycobacterial reemergence, and the emergence of antibiotic resistant microbial strains such as MRSA [64]. Microbial resistance occurs mainly in three general mechanisms: prevention of interaction of the drug with target; direct destruction or modification of the drug; and efflux of the drug from the cell [65]. These mechanisms were used by different microorganisms and led to the emergence of many pathogenic bacterial strains [64]. With pathogenic fungi, the situation is not so bright also, where Amphotericin B was for many years the only treatment available for fungal infections. In late 1980s fluconazole and itracozole was developed as additional therapeutic options [66]. Recently, azole derivatives are most widely used antifungal agents, although resistance for these drugs is emerging [67]. All the available antifungal drugs used to date are not ideal in efficiency, safety, and antifungal spectrum [68]. Combination antifungal therapy was also used to increase the efficiency but there is a real demand for a next generation of safer and more powerful antifungal agents [69]. Knowing that modifying known antimicrobial compounds is increasingly difficult created an urgent and very pressing need for isolation and identification of new bioactive chemicals from new sources including plants [70]. Plant derived natural products represent an attractive source of antimicrobial agents since they are natural, have manageable side effects and available at affordable prices [71]. Also plants derived agents may have different mechanisms than conventional drugs, and could be of clinical importance in health care improvement [72]. There are two main classes of plant derived agents.1) phytoalexins which are low molecular weight compounds produced in response to microbial, herbivorous, or environmental stimuli [73]. Phytoalexins include simple phenylpropanoid derivatives, flavonoids, isoflavonoids, terpenes and polyketides [74]. 2) Phytoanticipins which are produced in plants before infection or from pre-existing compounds after infection [73]. Phytoanticipins include: glycosides, glucosinolates and saponins that are normally stored in the vacuoles of plant cells [75]. The antimicrobial potential of plant derived natural products is well documented. Schelz and colleagues reported the potential of menthol isolated from peppermint oil to eliminate the resistance plasmids of bacteria [76]. In another study carbazole alkaloids isolated from Clausena anisata stem bark showed high antibacterial and antifungal activities [77]. Thousands of other phytochemicals having in vitro antimicrobial activities were also screened. Such screening programs are essential for validating the traditional use of medicinal plants and for providing leads in the search for new antimicrobial agents [78]. A number of studies of the bioactivity of plant extracts have been conducted and many of these studies showed promising results in developing new biologically active agents. The methanolic extract of clove Caryophyyllus aromaticus showed antibacterial activity against many bacterial genera and the highest activity was against Staphylococcus aureus [89]. Association of clove extract and antibiotics showed synergistic antibacterial activity against antibiotic resistant Pseudomonas aeruginosa [80]. Out of the 50 plants used in Indian traditional medicine, 72% showed antimicrobial activity including nine plants showed antifungal activity [81]. When some Palestinian plants were tested for bioactivity, out of fifteen used in traditional medicine, only eight showed antibacterial activity against eight different bacterial strains [82]. Butanol extracts of Rosa damascene, Narcissus tazetta, and Inula viscose exhibited potent antimicrobial activities against different microorganism including Methicillin-resistant

Staphylococcus aureus and Candida albicans [83]. During the past decade there is an increase in the number of immuno-compromised patients. This is probably due to the alteration of the immune system caused by human immunodeficiency virus (HIV), cancer chemotherapy, and organ and bone marrow transplantation in addition to the use of immune suppressors to treat many diseases [84]. The compromised immune system facilitates microbial infections including systemic mycosis. This leads to extensive use of Amphotericin B and azole derivatives as antifungal agents. Unfortunately, the wide range use of these antifungal agents leads to the emergence of drug resistant pathogenic fungi [84]. Candida albicans is opportunistic yeast that can cause vaginal, oral, and lung infections in addition to systemic tissue damage in AIDS patients [85]. This yeast was the target of many researchers to develop new antifungal agents. Out of twenty four medicinal plants used in traditional medicine in South Africa, two showed high potential to treat candidiasis [86]. Also some indigenous plants of Lebanon showed antimicrobial activity against Candida albicans and other tested microorganisms [87]. Successive isolation of antimicrobial compounds from plants depends upon the type of solvent used in extraction procedure [88]. Literature reported the use of different solvents to extract antimicrobial agents. The ethanol/methanol extracts of thirty four medicinal plants were more active than aqueous extracts against bacterial strains belonging to Enterobacteriaceae [88]. Methanolic extract of Terminallia chebula showed higher antibacterial potential compared with aqueous extract [71]. Mahasneh found that butanol extracts of several plants including: Lotus halophpilus, Pulicaria gnaphaloides, Capparis spinosa, Medicago laciniata, Limonium axillare to exhibit superior antimicrobial activity compared with ethanol and aqueous extracts [89]. The ethanolic extract of 11 plant species from Argentina showed high antimicrobial activity against a list of microorganisms including methicillin, oxacillin, and gentamicin resistant Staphylococcus [90]. Of 16 plants studied, the methanolic and aqueous extracts of 10 Yemeni plants exhibited significant antimicrobial activity against three gram positive, two gram negative bacteria, and one fungus [91]. Jordanian plants were the focus of many researchers for their antimicrobial activities. Butanol, ethanol, petroleum ether, and aqueous extracts were prepared from nine Jordanian plants. Butanol extract showed superior antimicrobial activity compared with other extracts [92]. Of 27 ethanol extracts prepared from indigenous Jordanian plants, six plants showed promising antimicrobial activity against different test microorganisms [93]. In addition to their broad antimicrobial activities some Jordanian plants like Sonchus oleraceus and Laurus nobilis exhibited high antiquorum sensing activities [94]. Other Jordanian plants like Crupina crupinastrum and Achillea biebersteinii showed high antimicrobial activity against bacteria and fungi [95]. Additionally the methanolic extracts of two Jordanian plants Artemisia herba-alba and Artemisia arborescens showed high antibacterial activity against 32 isolates of Mycoplasma species [96]

4. Medicinal Plants Oxidative Stress Antioxidant and Cancer

Various active compounds (or their semi-synthetic derivatives) derived from medicinal plants have been assessed for their efficacy and tolerability in the treatment of breast cancer. Active oxygen may cause cancer through two possible mechanisms: gene mutations and the effects on signal transduction and transcription factors. Oxidative stress causes damages to DNA, phospholipids, proteins and carbohydrates on the cell membrane. Oxidation and injury to DNA induce genetic mutation. The presence of free radicals may enhance the mutation of some genes. An antioxidant is "any substance that delays, prevents or removes oxidative damage to a target molecule" [97]. Antioxidants can act by diverse mechanisms in the oxidative sequence. The human body complex antioxidant defense system consists of the dietary intake of antioxidants, as well as the endogenous production of antioxidative compounds, such as glutathione, etc. [98]. Antioxidants can be classified into a number of different groups as enzymatic and non enzymatic strategies. The enzymatic antioxidant involve superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, while non enzymatic antioxidants include the vitamins A, C, and E, glutathione, and lipoic acid, mixed carotenoids, several bioflavonoids, antioxidant minerals (copper, zinc, manganese, and selenium), etc. Antioxidants may work either alone, or in association with each other against different types of free radicals. Vitamin E inhibits the propagation of lipid peroxidation; the combination of vitamin C and vitamin E suppress the formation of hydroperoxide; metal complexing antioxidant such as penicillamine inhibit free redical formation in lipid peroxidation [99]. Human body is constantly generating free radicals, which causes oxidative stress. Factors such as drugs, pollution, immune responses to viruses, deficiency of natural antioxidants, ultraviolet rays and tobacco destroy the body potential of stabilizing free radicals. In addition to those exogenous sources, endogenous sources of oxidative stress include mitochondria, or microsomes and peroxisomes, and enzyme NADPH. The body has the power to neutralize them, but if there is an imbalance between the free radicals and the ability of the body to neutralize it, it causes oxidative stress. Oxidative stress may cause various problems and diseases such as diabetes, Alzheimer's disease, Parkinson's disease, aging and cancer. Oxidative stress causes Lipid peroxidation in cell membranes, determined as free radicals, reacting with polyunsaturated fatty acids. Cell membranes contain polyunsaturated fatty acids (PUFAs) and lowdensity lipoproteins (LDL). They are sensitive to free radicals [100]. The interaction of ROS and lipids consists of three different steps: initiation, propagation and termination. The molecular oxygen reacts with carbon-centered free radicals, and thus, lipid hydroperoxides (LOOH) are formed. LOOH alter the membrane structure and function. Free redicals cause proteins oxidation. There are various markers of protein oxidation, which include protein carbonyl derivates, oxidized

amino acid side chains and formation of advanced glycation end products. In the oxidation process, Protein carbonyl derivates are formed early, and are generated as the peptide main chain as some amino acid side chains that are cleaved (arginine, lysine, or threonine), are oxidized [101-103]. The carbonyl groups are relatively stable [103], and may result in loss of protein function, as well as increased degradation of soluble proteins [101]. Protein oxidation has also been shown to be a chain reaction and may be inhibited by chain-breaking antioxidants [104]. Oxidation of proteins may develop some problem, but protein damage can be repaired, and is a non-lethal event for the cell [105]. DNA is especially sensitive to damage due to its potential to create cumulative mutations, which may disrupt cellular homeostasis [106]. DNA may be damaged by ROS and cause permanent structural changes in, as base-pair mutations, deletions, insertions, rearrangements and sequence amplification [107]. Continuous oxidative damage to DNA may lead to alterations in signaling cascades or gene expression, and may cause replication errors and genomic instability [106]. In recent years, oxidative stress and the mechanisms by which cancer is caused has been extensively studied. Cancer development is a multistage process which involves mutations in critical genes required for maintenance of the cellular homeostasis [106]. Oxidative stress causes initiation, promotion and progression of carcinogenesis [108]. ROS play an important role in the development of cancer. Oxidative damage to DNA or of antioxidant defense systems leads to mutation, activated transcription factors, modification of gene expression and chromosomal aberrations, processes which have been described as the agents of progressions of cancer. Inflammation also causes DNA mutaion [109]. 25% of all cancers in the world is due to chronic inflammation due to infection or injury [110]. Various chemicals such as chlorinated compounds, metal ions, aromatic hydrocarbons and some peroxisome proliferators have been shown to induce oxidative stress, which damages the DNA. They may, therefore, partly account for the development, especially of workrelated cancers. Many cancers are associated with increased production of ROS [108]. Natural products, especially plants, have been used for the treatment of various diseases from ancient times. People of Egypt, China, India and Greece have been using terrestrial plants as medicines, and a large number of modern drugs have been developed from them. Medicinal plants have been used in the treatment of many diseases, such as diabetes, obesity and cancer, etc. There are many evidences that the generation of free radicals inside the body cause damages to DNA and lead to the development of cancer, etc., and if these free redicals are neutralized by the antioxidants from different medicinal plants, then it prevents cancer. Several studies have shown that plant derived antioxidant scavenge free radicals and modulate oxidative stress. Free radicals are the cause of many diseases such as cancer, atherosclerosis, diabetes, neurodegenerative disorders and aging; different experimental and clinical studies have proved that higher intake of antioxidant rich food is associated with decreased risk of cardiovascular diseases and cancer. The free radical neutralizing property of several plants have been screened by various researchers. Plants have been used in the treatment of cancer. The National Cancer Institute collected about 35,000 plant samples from 20 different countries, and has screened around 114,000 extracts for anticancer activity. 60% of the commercialy available anticancer drugs are from natural sources. Treatment by herbal medicines may have some advantages over treatment by single purified chemicals [111]; as hebal medicine are the mixtures of more therapeutic or preventive components, and so might have more activity than single products alone. The antioxidant and anti-tumor effects of extracts from various herbs and medicinal plants have been proved experimentally and clinically. Several in vitro or in vivo studies have proved the anticancer potential of the extracts from several medicinal plants [112-114]. Experimental studies of aqueous extracts from willow (Salix sp.) leaves show prevention of proliferation of cancer cells [114]. Ganoderma lucidum methanolic extracts induced apoptosis in human breast cancer cells Hu et al. [113] and Kao et al. [115] studied that an aqueous extract of Bu-Zhong-Yi-Qi-Tang (a mixture of ten herbs), had the ability to induce apoptosis in hepatoma cells. Most of the plants contain phenolic and flavonoid compounds, which have antioxidant activities, and thus, prevent oxidative stress and cancer [116]. The effect of an aqueous extract of Paeoniae lactiflora were studied on HepG2 and Hep3B hepatoma cells, which showed apoptosis. Yano et al. [117] stated that aqueous extract of Sho-Saiko-To caused inhibition of the proliferation of KIM-1 human hepatoma cells. It was stated by Bonham et al. [112] that PE-SPES (mixture of eight herbs) had been used as a clinical treatment of prostate cancer. Chemical and diferent studies of various extracts from the herbs were found to to be useful in preventing radiation damages and purify blood quality [118,119]. The seeds of Luffa aegyptiaca has the ability to destroy the human metastatic melanoma [120].

5. Medicinal Plants in Clinical Use

The anticancer agents, vinblastine and vincristine from the Madagascar periwinkle, Catharanthus roseus G. Don. (Apocynaceae), introduced a new era of the use of plant material as a medication for treatment. They were the first agents to advance into clinical use for the treatment of cancer. Vinblastine and vincristine are used in combination with other cancer drugs, for the treatment of various kinds of cancers, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers The isolation of paclitaxel (Taxol®, 3) from the bark of the Pacific Yew, Taxus brevifolia Nutt. (Taxaceae), is another good step in the discovery of natural product drug. Various parts of Taxus brevifolia and other Taxus species (e.g., Taxus Canadensis Marshall, Taxus baccata L.) have been used by several native American tribes for the treatment of various diseases, while Taxus baccata was reported to use in India as a medicine for the treatment of cancer. The paclitaxel was clinically introduced to the US market in the early 1990s. Paclitaxel is

active against a number of cancer types, for example: ovarian cancer, advanced breast cancer, small and non-small cell lung cancer. Camptothecin was isolated from the Chinese ornamental tree, Camptotheca acuminate Decne (Nyssaceae), the clinical trials in the 1970s dropped it because of severe bladder toxicity. Derivatives of camptothecin, Topotecan and irinotecan, are used for the treatment of ovarian and small cell lung cancers, and colon cancers, respectively.

6. Conclusions

The potential isolation and use of new and novel bioactive products from plant origins is still very productive playground for the development of new drugs to improve health care in certain medical fields. Free radicals are the cause of oxidative stress, which may causes injury to cells, gene mutation, and may lead to cancer. Oxidative stress causes cancer, by the interaction with intracellular signal transduction and transcription factors, directly or indirectly. Medicinal plants are main sources in healing of the cancer around the world. This property of the plants is because of the presence of potent anti cancer substances. Medical plants treatment of cancer is prevalent, especially in our country where resources are limited. Several medicinal plants have been known to cure and control cancer. Most of the medications used word wise contains herbal product, with no side effects. It is essential to emphasize that extensive in vitro and in vivo tests must be conducted to assure the selection of active and nontoxic anticancer and antimicrobial phytochemicals.

Authorship Contribution

All authors contributed to the design, preparation, editing, and final review of the manuscript.

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