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Anticancer Activities of Green Synthesized Copper Oxide Nanoparticles: Recent Review

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Keywords: Copper oxide NPs (CuO-NPs); Green synthesis; anticancer activity.

Abstract

Nanotechnology and Nanoscience is a multidisciplinary field to exploit the wide spectrum of the emerging area from fundamental sciences with novel techniques. Nanoparticles have greater surface area to volume ratios. Up to now, numerous biological organisms are described to have their potentiality for the synthesis of metallic nanoparticles. Green synthesis is a gradually evolving research area that used to extract nanoparticles from plants. Natural products have a long history of use in the treatment of cancer. Cancer is a group of diseases involving abnormal cell growth with the ability to spread the other parts of the body. Cancer is often treated with some combination of radiation therapy, surgery, chemotherapy, and targeted CuO-NPs made of the plants, which have anticancereous properties, which can counteract the symptoms as against the cancerous cells. Different chemical and physical methods have been proposed to synthesize CuO-NPs. Among those methods, the green synthesized NPs have significance in safety and eco-friendly nature. The green synthesized CuO-NPs showed promising anticancer activity against different cancer cell lines. In fact, green synthesized CuO-NPs are an effective candidate for pharmaceutical, biomedical, and environmental applications. To explore the anticancer potential of the CuO-NPs plants extracts for isolation and characterization of the active anticancer principles so that better, safer and cost effective drugs can be developed for treating cancer.

Introduction

Nanotechnology and Nano science is a multidisciplinary field to exploit the wide spectrum of the emerging area from fundamental sciences such as physics, chemistry electronics, and material science with novel techniques and produces unusual and unique properties of a nonmaterial at Nano range [1,2]. Nanoparticles are a number of atoms or molecules bonded together and are intermediate in size between individual atoms and aggregates large enough to be called bulk material [3,4].

Nanotechnology is the process of matter for the use in specific applications through certain physical or chemical processes to yield materials having nano-sized magnitudes in the range of 1-100 nm with the specific properties. Nano science is gaining much importance nowadays as the properties such as quantum, mechanical and thermodynamics, which are not visible on the macroscale, are accessible on nanometres scale. New materials with remarkable characteristics can be formed by placing molecules with desired properties together. Nanoparticles have better surface area to volume ratios than larger particles. This causes them to be more reactive and interactive than other materials. Nanoparticles have vast applications in the field of biomedical, electrical, environmental engineering fields, etc. [5].

The nanotechnology is well-thought-out to be the next industrial uprising, the search is immobile ongoing for better non-toxic and eco-friendly approach for synthesis of nanomaterials [7]. The use of plant extracts for the synthesis of nanoparticles is a progressively growing research area is a green synthesis of NPs [8]. In contrast to chemically synthesized nanoparticles, green synthesized nanoparticles are more effective and eco-friendly [9]. Nowadays numerous biological organisms are reported to have their potentiality for the production of metallic nanoparticles. Though, the rate of metal nanoparticle synthesis with the help of plant extract is stable [10], much faster [11,12], and extremely mono-dispersive [13], in respect to other biological methods.

All of the drawbacks presently associated with available chemotherapeutic agents are needed to search for newer, more efficacious, and better-tolerated drugs. Natural products, suggestion an unlimited tank for examination. Preparations of the plant are used in the treatment of ear and eye infections, inflammation (leaf juice); tooth ache (fruit juice together with fluid from snails); fever, headache, and cold (fume from burning leaves inhaled); cough, pain, inflammation, infections, convulsion, diarrhoea, and as stimulating tonic (root decoction) [14]. Plants have a long history of use in the treatment of cancer. Activities of plant extracts had been reported [15,16].

Cancer is one of the main causes of death globally. The prevalence of this disease is rising, however, more rapidly in Africa, Asia, and Central and South America that make up about 70% of cancer deaths in the world [17]. Cancer is a disease of multicellular organisms [18]. Characterized by uncontrolled multiplication of subtly modified normal human cells [19]. Cancer is a leading cause of death all over the world and represents a major public health problem [20]. Cancer is the first leading cause of death in economically developed countries and the second leading cause of death in developing countries [21].

The burden of cancer is growing in economically developing countries as a result of population aging and growth as well as, increasingly, an adoption of cancer-associated lifestyle choices including smoking, physical inactivity, and “westernized” diets [22]. It has been estimated that the total number of new cases of cancer will increase from 10 million in year 2000 by roughly 25% in each decade, reaching 24 million new cases per year in the year 2050; the total number of deaths will rise from 6 million in the year 2000 to 10 million in 2020 to over 16 million in the year 2050; in the year 2050, there will be 17 million new cases of cancer in less developed countries, while only 7 million new cases of cancer will occur in the more developed countries [23,24]. By 2030, it is estimated that there will be 26 million new cancer cases and 17 million cancer deaths per year [25].

Nowadays, breast cancer persists to be the most important cause of death globally [26]. Hence, the continuing search for anticancer agents/compounds from plants played a critical role to find the possible ways to have safe and to decrease the side effects induced by chemotherapy since natural herbal medicines have many advantages [27,28].

Over the years, different methods have been working and are still in use, independently as well as in combination, in the treatment of cancer. Surgery and radiation therapy are used to treat localized cancers, while as chemotherapy treat cancer cells that have metastasized to other parts of the body because they travel throughout the body in the bloodstream [29].

According to the reports, the use of existing chemotherapy drugs has their problems such as high cost, maliciousness, and severe side effects. It is essential to discover alternative therapies, Nano drugs, and Nano formulations for drug delivery to conquer the situation. The proper combination of nanomaterial and biology will not only toughen the fight against pathogenic microorganism but can also render an outcome toward combating infectious diseases [30]. Green chemistry is sustainable chemistry, used to minimize the generation of hazardous substances [31]. Green synthesis of metal oxide NPs is one of the simplest and eco-friendly approaches, among which natural product mediated synthesis has paying attention remaining to its nontoxicity and also being an economical and simplistic process [32].

In the broad-spectrum of biologically active NPs, metal NPs such as Ag, Au, and Cu are the most sought after nanomaterial and increasingly used in medical and consumer products because of their high surface to volume ratio with small dimension [33,34].

Recently, metal oxide NPs as an antimicrobial and anticancer agent has drawn considerable interest as a result of their large applicability in various industrial fields and biomedical applications. Up to date, despite the great progress in nanotechnologies, there is still a lack of definite knowledge on the effects of CuO-NPs on cancer cell lines. The earlier history of NPs research demonstrations looks to have relative toxicity to cancer cells, without affecting the healthy cells. Remarkable attention is focused toward CuO-NPs as it is approximately 10-fold cheaper than silver and gold in the market and therefore, a method utilizing CuO would prove to be quite cost-effective. Moreover, CuO-NPs have been examined as antibacterial agent against Gram-negative and Gram-positive microorganism and have high sensitivity even in the low concentration of CuO-NPs; it is of special interest to view CuO-NPs as anticancer agent, as well as an inorganic disinfectant [35,36].

CuO-NPs have acquired great interest in research fields, such as solar cells, [37] biodiesel, [38] photo catalysis, [39] water pollutant removal, [40] Super capacitors, [41] electro catalysis, [42] etc. due to their desirable properties such as low cost, nontoxicity, and easy preparation [41]. The number of electro catalytic applications of CuO-NPs has been limited in spite of the methods offering improved sensitivity and selectivity and being more economical.

CuO-NPs have received much consideration because of are the simplest members of the family of copper salts, and they possess a range of convenient physical properties such as electron correlation effects, spin dynamics and high temperature superconductivity [43]. Copper is one of the crucial microelements, which is very essential for the growth of plant. It can be present as Cu2+ and Cu+ under natural conditions. Optimum concentration is commonly involved in the plants, ranging from 10-14 to 10-16 M. In addition to many of its main purposes such as protein regulation and cell wall metabolism, it also acts as secondary signalling molecule in plant cells. It plays crucial role in the photosynthetic electron transport, mitochondrial respiration, iron mobilization, hormone signalling, oxidative stress response, and also acts as cofactor for many enzymes [44,45]. Moreover, in the case of copper, different organisms such as microbes [46,47], algae [48], fungi [49,50], and angiosperm plant extracts [51,52], are utilized for the nanoparticles production.

Copper oxide is a p-type semiconductor with a narrow band gap (1.2eV) and has been subjected to extensive investigations for its prospective applications in various fields such as gas sensors, catalysis, batteries, high-temperature superconductors, solar energy conversion, photovoltaic devices and field emission emitters [53,54].

The 'green synthesis' of nanoparticles (NPs) using plant is advantageous over chemical, physical and or microbial synthesis as it removes the complicated protocol; and can also meet the large-scale production requirement [55]. Different chemical and physical methods have been proposed to synthesize CuO-NPs such as hydrothermal synthesis, [56] sonochemical synthesis, [57] sol-gel method, [58] thermal decomposition [59], colloidal thermal synthesis, [60] microwave irradiation, [61] thermal decomposition, [62] solution method, [63] and quick-precipitation method [64, 65]. Among these methods, hydrothermal and quick precipitation methods have significance in safety and eco-friendly nature. Quick-precipitation is especially more attractive because of its fast, convenient, ease of mass production, cost-effectiveness, and environmentally friendly path to produce CuO-NPs.

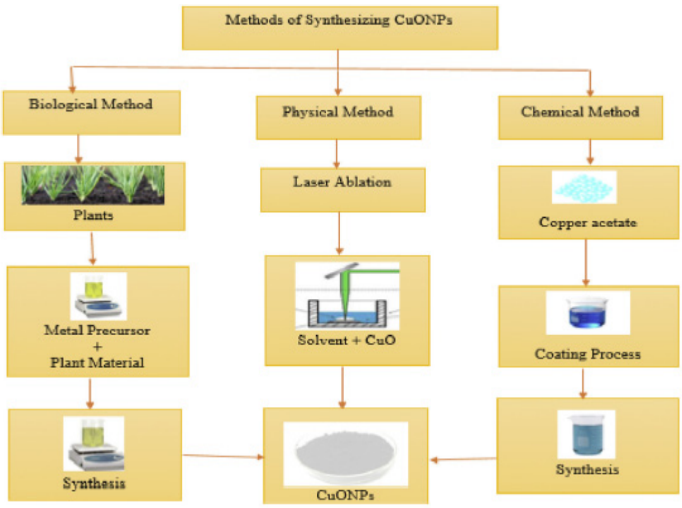

Figure 1: Flow chart representing the various methods of synthesis of CuO NPs [66].

The synthesized CuO-NPs were evaluated using UV-visible (UV-vis) spectroscopy, Fourier Transform Infrared (FT-IR) spectroscopy, Thermogravimetric Analysis-Differential Thermal Analysis (TGA-DTA), X-Ray Diffraction (XRD) spectroscopy, X-ray Photoelectron Spectroscopy (XPS), Scanning Electron Microscopy (SEM) and electrochemical studies [67]. The unique properties of CuO-NPs and their potential applications have continued to attract a lot of attention [68]. CuO-NPs are used to improve viscosity of energy transferring fluids, thereby boosting thermal conductivity [69]. In industrial fields, CuO-NPs are widely used as p-type semiconductors and transistors in the design and production of batteries [69], solar cells [70], gas sensors [71] and field emitters [72]. Nowadays, CuO-NPs are utilized as heterogeneous catalysts [72], antioxidants, drug delivery agents, and imaging agents in field of biomedicine [67-68]. The plant extract may act as an anti-hyperglycemic [73] and also have some curative role against influenza and tuberculosis [71]. The plant is a rich source of various terpenoids, carbohydrates, phenols, and flavonoids [74,76]. On the other hand, despite other inorganic applications, nanomaterials are utilized as an antimicrobial agent and defence booster in the field of agriculture.

The Plant Kingdom produces naturally occurring secondary metabolites, which are being studied for their anticancer activities leading to the synthesis of new clinical drugs with the success of these compounds that have been developed into staple drugs for cancer treatment.

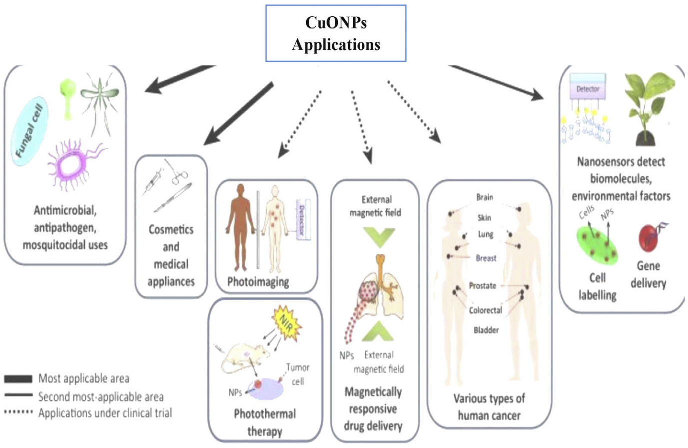

Figure 2: Flow chart showing some applications of CuO-NPs [66].

In this context, here, an attempt has been made to review recent synthesized copper oxide nanoparticles in an eco-friendly, greener route by using the important different variety of plant extract. The potentiality of these CuO-NPs to review recent anticancer activity and generation of stress has also been checked in a model plant.

This review of CuO-NPs discusses the demand for naturally derived compounds from medicinal plants and their properties, which make them targets for potential anticancer treatments. Various plants in which CuO-NPs can be synthesized from are used to review anticancer activity.

Anticancer activities of some green synthesizes CuO-NPs

Aloe barbadensis

Several naturally produced herbal formulations are currently available for cancer patients. As most of chemotherapeutic agents were cytotoxic to normal cells and developed drug resistance [77]. Vera, which revealed anticancer and cytotoxic activities against neuroectodermal tumors, lung squamous cell carcinoma and hepatoma cell. *C. comosum* also, has been exhibited anti- inflammatory, anti-ulcer and anti-cancer activities in rat and shrimp animals model Dehydrodicatechin A is an active component of *C. comosum*, which inhibits the growth of Ehrlich ascites [78].

Figure 3: Aloe barbadensis.

Azadirachta indica

Uncontrolled cancer cell growth and proliferation are one of the fundamental hallmarks in cancer and play important role in the development of tumour and cancer metastasis [79,80] Therefore, inhibiting the growth of tumour cells is a common feature of many chemo preventive and therapeutic agents. Extracts of neem suppress the proliferation and growth of tumor cells through disruption of cell cycle progression. For example, neem seed oil inhibits growth of HeLa cervical cancer cells [81], and NLE shows proliferation inhibitory effects in prostate cancer cells [82].

Besides inhibiting cancer cell proliferation, neem components exert anticancer effect by induction of apoptosis as well as other forms of cell death including autophagy. Extracts from seeds and leaves of neem induce apoptosis in different types of cancer cells such as leukemia, prostate [83] cervical [84], colon [85], stomach [86], and breast as well as choriocarcinoma [87], and hepatocarcinoma cells [88]. *Azadirachtin* shows similar effect in cervical cancer cells [89]. Proapoptotic members (e.g. Bax and Bad) and antiapoptotic members of the Bcl-2 family (e.g. Bcl-2 and Bcl-xL) regulate this cytochrome c release. Thus Bcl-2 family proteins are significant marks for applying anticancer effects of neem in cancer cells. For example, neem-induced apoptosis in prostate cancer cells is mediated by the concurrent decrease of Bcl-2 and increase of Bax levels [89]. Apoptosis or cell death is a very complex process involving multiple groups of protein, thus targeting multiple components in the apoptotic pathway is likely to improve the anticancer efficacy of neem components or extracts.

Figure 4: Azadirachta indica.

Glycyrrhiza glabra

The findings of this study were LA induced modest level of apoptosis but had more pronounced effect on cell cycle progression arresting cells in G2/M, accompanied by suppression of cyclin B1 and cdc2. It also inhibited phosphorylation of Rb, specifically phosphorylation of S780 with no change of phosphorylation status of T821, reduced expression of transcription factor E2F concurrent with reduction of cyclin D1, down-regulated CDKs and but increased cyclin E expression. These findings provided explanation for LA activity and suggested that it might be considered as a chemo preventive agent [90]. Isoliquiritigenin was a candidate agent for the treatment of prostate cancer and GADD153 might play an important role in isoliquiritigenin-induced cell cycle arrest and cell growth inhibition [91].

Figure 5: Glycyrrhiza glabra.

Curcuma longa

The anticancer activity of turmeric when evaluated prophylactically and therapeutically i.e., pre-induction treatment and post-induction treatment respectively by two different routes of administration i.e., per oral and topical application. Though post-induction per oral treatment with turmeric demonstrated a significant anticancer activity against MNU-induced mammary cancer in rats, the degree of anticancer activity was more prominent in prophylactic treatment groups and was more effective particularly with topical application. It was clearly evidenced by the decreased drastic reduction in mean tumor volume and higher degree of tumor growth inhibition in prophylactic topical application of turmeric when compared to the therapeutic treatment of groups. This study demonstrated similar results with the previous work reported [92].

Prophylactic topical application of turmeric has shown superior efficacy when compared to all other groups in reduction of the incidence rates of tumor induction, prolongation of mean latency periods of tumor development, reversal of mean tumor volume and inhibition of tumor growth. Hence, interesting findings in curcuma longa i) Preventive role of turmeric against MNU induced mammary cancer was more predominant than the therapeutic role of turmeric on MNU induced mammary cancer [93]. Its antiproliferative effect is estrogen dependent in ER (estrogen receptor)-positive MCF-7 cells and estrogen independent in ER-negative MDA-MB-231 cells [94].

Figure 6: Curcuma longa.

Camellia Sinesis

Several mechanisms involved in GTCs inhibition of cancer formation/progression are recently reviewed by numerous Authors [95,96]. Certainly, GTCs, through their antioxidant activity, are capable to reduce ROS and chelate transition metals, formed during all the carcinogenesis stage. However, it has been reported that also GTCs can be a source of ROS generation, inducing oxidative stress and consequently activating apoptotic pathways [97].

Inhibition of Cell Proliferation and Cell Cycle Arrest. GTCs exhibit ant-proliferative effects against both androgen sensitive and androgen-insensitive human PCa cells. The effect is mediated by cell cycle deregulation and cell death induction [98].

Figure 7: Camellia sinesis.

Table 1: Anticancer activities of some green synthesized CuO-NPs on cancer cells.

No	Name of plant used in Green synthesis	Part of Plant used	Cancer cells	Anticancer activity	References
1	*Acalypha indica*	Leaf	HCT-116	Excellent	106
2	*Azadirachta indica*	Leaf	MCF-7	Excellent	107
3	*Brassia actinophylla*	Flower	HT-29	Excellent	108
4	*Momordica cochinchinensis(Lour)*	Leaf	HepG2	V. good	109
5	*Chaetomorpha*	Seaweeds	MCF-7,	High	110
			MDA-MB-231	Excellent	

Some of the recent reports on synthesis of CuO NPs using plant sources include the use of Saraca indica with fluorescence properties, [99] Aglaia elaeagnoidea with catalytic and recyclability properties [100]. Fortunella japonica for electrocatalytic detection of 4-nitrophenol [101]; Rheum palmatum. root extract for catalytic reduction of 4-nitrophenol [102], Madhuca longifolia for waste water treatment, [103] Tridaxprocumbens leaf extract for mosquito larvicidal activity, [104] and synthesis of ultrasmall copper nanoparticles using lemongrass tea extract [105].

The summary of Table 1 indicates that, anticancer activities of different aerial part of natural product extract via green synthesized CuO-NPs on cancer cells shows as a promising candidate to synthesize anticancer drugs for cancer treatment.

Conclusion

Cancer is listed in one of the high profile disease in developing and developed countries. As per WHO report of 2018, 9.5 million people died from cancer related diseases. The majority of death rate is from people living with in low-income countries. Therefore, the demand for prevention and therapy of cancer is extremely high. Chemically-sythesized drugs have been developed and other cancer treatments pre-exist. However, current methods, such as Chemotherapy is accessible for treatment of cancer, but have their own limitations due to their toxicity on non-targeted tissues furthering human health problems. Therefore, there is a necessity for alternative treatments with CuO-NPs anticancer agents with plants being the desired source. Increasing demand for green synthesized plants is putting pressure on high-value CuO-NPs. CuO-NPs anticancer agents are effective inhibitors of cancer cells lines, making them in high demand. The CuO-NPs showed promising prospect for anticancer activity against cancer cell line. In general, due to its environmental and biomedical applications, green synthesized CuO-NPs are an effective candidate for treatment of cancer diagnosis.

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