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A review on terpenes for treatment of gastric cancer: current status and nanotechnology-enabled future†

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Eighty-five percent of gastric cancer is caused by *Helicobacter pylori* infection. Delays in detection, limited efficacy, and significant side effects of the available treatments lead to a 5-year survival chance of only 32%. Therefore, better remedies are required. Numerous studies have been published on herbal medications offering an edge over conventional medicines. Secondary metabolites such as different polyphenolic compounds including terpenes are key players for therapeutic advantages. The antimicrobial, anticarcinogenic, anti-inflammatory, *etc.* activities of biocompatible active ingredients make these compounds suitable for therapeutic use. Despite such advantages, the use of herbal medicine in gastric cancer treatment is limited. In this article, we describe the therapeutic potential and limitations of terpenes followed by the potential advantages offered by the combinatorial effects of terpenes with their nanoconjugates. These include increasing the anticancer and antimicrobial potency of drugs as well as resolving drawbacks including targeted delivery, stability, half-life, *etc*, thus making them suitable for gastric cancer treatment. The article concludes with a detailed discussion on the challenges encountered in deploying targeted secondary metabolites and their future developmental prospects to provide ideas and insights for future research.

Sustainability spotlight

Globally, cancer is the second most deadly disease after heart disease. Among all forms of cancer, gastric cancer is the 4th most deadly after lung, breast, and colon cancer, costing 769 000 lives in 2020, with more than 1.09 million new cases being diagnosed. *Helicobacter pylori* is associated with ∼85% of the tumors. *H. pylori* infection is directly linked to the population with a poor economy and hygiene, and so is gastric cancer. This review deals with managing gastric cancer with natural products such as terpenes. Nature is full of resources in the form of secondary metabolites that humankind has used for a long time to manage many diseases, including gastric cancer. Many of these herbal formulations are already in use in different forms of medicine, such as Ayurveda, Unani, Siddha, and homoeopathy. Terpenes are a diverse group of compounds consisting of around fifty-five thousand members, of which many have selective anticancer, anti-microbial, and anti-inflammatory properties. Due to their abundance, fewer side effects, and cost-effectiveness, they have been popularised in traditional medicines. But problems such as low stability, solubility, and shelf life restricted their use in modern medicine. This review describes the potential role of terpenes in gastric cancer management. It suggests how terpenes may be explored in the development of practical, safer, cheaper, and sustainable modern medicine with the help of nanomedicine.

1. Introduction

Globally, cancer is the second most deadly disease after heart disease.[1] In cancer, the body cells lose the property of normal division and undergo uncontrolled division giving rise to abnormal cells that collectively leads to tumor formation.[2] The primary causative agents of cancer are ultraviolet radiation or ionizing radiation, bacterial infections, viral infections, parasitic infections, *etc.*[3]. Among different forms of cancer, gastric cancer is the 4th most deadly after lung, breast, and colon cancer, costing 769 000 lives in 2020, with more than 1.09 million new cases being diagnosed.[4,5] The primary cause of gastric cancer is infection with *Helicobacter pylori* (*H. pylori*),[6] a Gram-negative, microaerophilic, motile, flagellated spiral-

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shaped bacterium associated with 70–85% of gastric cancer and considered a type I carcinogen for the disease. It is the most common etiologic agent that is associated with other cancers, such as duodenal cancers (90–95%), and is responsible for 25% of all infection-associated cancers.[7] Its pathogenicity is due to its genes, including *CagA*, *VacA*, *BabA*, *SabA*, *OipA*, *DupA*, and *FlaA*.[6] Approximately half of the world's population is infected with *H. pylori*, and most such colonized individuals develop coexisting chronic inflammation. Apart from *H. pylori*, various other factors, including smoking and consumption of tobacco-related products, a low-fiber diet, long-term stomach inflammation, obesity, family history, and a diet high in salty and smoked foods, increase the risk of gastric cancer.[8]

Unfortunately, in most cases, the diagnosis of gastric cancer is delayed due to the absence of early specific symptoms and the five-year survival rate is only 15%.[9] This low rate is despite different treatment modalities for gastric cancer, such as chemotherapy, surgical treatments, radiation therapy, and immunotherapy. Therefore, prevention is a more efficient way of gastric cancer management than treating it. Furthermore, available treatments involving modern chemotherapeutic agents show many side effects, including hair and weight loss, diarrhea, anemia, blood clots, and heart, kidney, and liver damage, compromising the patient's quality of life.[10] Furthermore, the effectiveness of surgery and radiation therapy is primarily limited to the early stages of gastric cancer progression.[11] An alternative approach to managing the disease is thus urgently needed. One potential alternative is the use of herbal formulations. To understand their viability, a brief look at the role of inflammation and the body's natural response to it is in order.

From any damaging stimuli such as pathogens, wounds, foreign bodies, or infection, a biological response of inflammation ensues.[12] The organism tries to self-protect or remove that inflammation using a natural body process – self-defense. In many cases, the body produces cytokines against a particular disease or foreign substance. In a few instances, these cytokines are overexpressed by the body's immune system. Gastric cancer is one of the best examples of human inflammation-associated cancer.[13] Synthetic anti-inflammatory drugs are being used to suppress or inhibit these mediators.

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These synthetic drugs have benefits and side effects that compromise patients' quality of life. For this reason, currently, people are expecting or even preferring treatments that involve natural products with safe toxicological profiles, leading to the exploration of these for alternative drug delivery treatments.[14]

Nature is full of resources in the form of secondary metabolites that humankind has used for a long time to manage many diseases, including gastric cancer. The formulations are well documented in few cases, but additional documentation is needed for most. Many of these herbal formulations are already in use in India, China, Vietnam, and Africa, in various forms through different systems of medicine such as Ayurveda, Unani, Siddha, and homoeopathy.[15] These medicines are mostly a mixture of various plant secondary metabolites, including phenolics, alkaloids, saponins, terpenes, sterols, and sphingolipids. For example, in many plants, the extract has anti *H. pylori* activity, suggesting their potential for treating gastric cancer. In addition, many of the compounds present in such herbal formulations can be administered orally to work on the target site without being absorbed by the intestine or stomach. The net result is targeted delivery and site-specific activity, which increase their potential for treatment with reduced side effects. In other words, herbs play a crucial role in controlling the growth and progression of cancer and can help patients overcome the side effects caused by chemotherapeutics. They enhance the body's immunity through naturally occurring compounds in them and thus prevent the spread of cancer by any means, including growth, metastasis, and invasion. Therefore, using these formulations instead of radiation and chemotherapy will be a better option as they do not cause any of the ill effects that conventional therapies cause, such as fatigue, hair loss, mouth sores, nausea, vomiting, and organ failure.[16]

In this framework, a class of natural compounds named terpenes, a highly diverse family of natural products, has drawn attention due to their capability of selectively killing tumor cells without hampering normal cells. These are synthesized by plants and are also called secondary metabolites. Terpenes have 55 000 members with different chemical structures and curing potentials.[17] They suppress or inhibit the growth of several cancers, such as breast, skin, stomach, pancreatic, colon, and prostate, without damaging or contributing any toxicity to normal cells as they exhibit pleiotropic actions by acting on a target in multiple ways. They also inhibit protein synthesis by targeting the main events crucial for the process. They are among the leading herbal formulations in cancer treatment and are discussed in detail in Section 2. However, despite the remedial effect and other advantages such as biocompatibility, safety, non-invasiveness, convenience, and low cost in the treatment of cancer as compared to conventional chemotherapy,[18] many natural formulations, including terpenes, have not been widely deployed in modern medicine due to certain problems associated with their transport across the body. Conventionally, they are given as such *via* different ways through food or in the form of supplements or directly as herbal medication but they have certain pharmacological and chemical issues associated with them such as low water solubility, low permeability, stability, reduced bioavailability, sensitivity to environmental conditions (temperature, pH, and humidity), chemical degradation or volatilization being a few of them.[19] This is precisely where nanotechnology can help overcome these disadvantages of herbal medicines.

Dr Diptiman Choudhury is an Associate Professor and co-leader of the Centre for Cancer Detection and Treatment at the TIET-VT Center of Excellence in Emerging Materials. After finishing his PhD at the University of Calcutta, Kolkata in 2012 Dr Choudhury joined for his Post-doctoral research at Cedars Sinai Medical Centre, Los Angeles. Dr Choudhury joined TIET in 2015. Dr Choudhury has a deep interest in Cell and Molecular Biology, Cancer Biology, Wound Healing and Drug Delivery. The main focus of Dr Choudhury's research work is to make medicines and medical technology safer. Dr Choudhury has published more than 40 SCI papers, 3 patents, and 5 book chapters so far.

Nanotechnology involves the utilization of critical properties of materials at the nanoscale. It consists of developing nanomaterials between 1–100 nm by manipulating the structures at the atomic level. Nanomaterials have unique electrical, optical and magnetic properties and a large surface area to volume ratio and are governed by the laws of quantum mechanics.[20] Due to their large surface area to volume ratio, they exhibit specific properties such as enhanced catalytic activity, biological activity, non-linear optical performance, and thermal conductivity. They can be delivered as liposomes, vesicular systems, nano-emulsions, nanostructured lipid carriers and solid lipid nanoparticles. Moreover, the use of these terpenes in the form of nano-formulations has been shown to enhance their solubility, stability and bioavailability, anti-proliferative activity, prevention from biological and chemical degradability and cell toxicity, enhanced specificity and pharmacological activity, and improved distribution of tissue macrophages along with sustained release.[21–23] Nano-delivery systems have been used to deliver all the herbal compounds irrespective of their hydrophobic or hydrophilic nature and thus can be used for transfer of hydrophobic terpenes *via* encapsulating them with nanoparticles which enhance their potency. Some of the terpenes are generally recognised as safe penetration enhancers. As a result, they can serve as excipients for other drugs or phytochemicals and make them suitable for administration through topical routes.[19] For instance, the bioavailability of celastrol was increased after loading it into poly (ethylene glycol)-block-poly(ε-caprolactone) nano-polymeric micelles. These micelles play a crucial role in inhibiting the growth of SO–Rb 50 retinoblastoma in a mouse xenograft model in a dose dependent manner. The nano-encapsulated celastrol was found to exhibit the antitumor activity by reducing the expression of Bcl-2, NF-κB, and phospho–NF–κB p65 proteins at 54.4 μg ml^{-1} after 48 h of the treatment.[24] The anti-proliferative activity of celastrol loaded poly(ε-caprolactone) nanoparticles (CS-NPs) has also been examined using different prostate cancer cell lines (LNCaP, DU-145, and PC3) by exposing the cells to a 0.5–2.0 μM concentration of CS-NPs.[25] The results showed inhibition of concentration-dependent proliferation. In a nutshell, nanotechnology has fundamentally changed the way many diseases, including gastric cancer, are diagnosed and treated. To this end, in this review article, we focus on different active natural terpenes obtained from natural sources, their role in controlling gastric cancer, and directions for future research in gastric cancer management.

2. Natural terpenes for treating gastric cancer

An active area of global research is to develop effective anticancerous products from natural materials such as medicinal plants or effective medicinal components.[26,27] Of all the available human medications, one-third are derived from herbal plants or extracts. Based on their positive aspects, their consumption is encouraged by physicians and researchers. Apart from cancer, they are widely used in different applications. Several dietary products such as fruits, vegetables, cereals, and spices exhibit anti-cancerous activity to a great extent, and it was found that there is an inverse relationship between the intake of natural products and cancer cases.[28–30] The primary factor responsible for this salutary action is the presence of different phytochemicals, which promote various mechanisms to prevent gastric cancer. The effective means for gastric cancer are cell proliferation or *H. pylori* inhibition, autophagy, apoptosis, anti-angiogenesis, or suppressed cell metastasis.[30–32]

2.1 Natural terpenes and their role in gastric cancer treatment

Terpenes are the largest and most diverse category of naturally occurring family of ~30 000 different polymeric compounds made up of isoprenes, or 2-methyl-1,3-butadiene ($(CH_2{=}C(CH_3){-}CH{=}CH_2)_n$ where n is the number of isoprene units (where $n \geq 2$). Terpenes play an essential role in plants' defense mechanisms, protect them from herbivores, and generate disease resistance. They play different roles in plants, including serving as thermoprotectants and performing signaling and medicinal functions. They also work as solvents or flavoring agents.[33] In addition, they have antimicrobial, anticarcinogenic, anti-inflammatory, antiallergic, and neuroprotective properties.[34] Not surprisingly, numerous studies have shown that they play an equally essential role in supporting human health.

Based on the number of isoprene units, they are classified into monoterpenes, diterpenes, triterpenes, and sesquiterpenes.[33] A brief description of these follows.

2.2 Monoterpenes

They comprise a large group that performs numerous biological activities and act as antioxidants, anti-inflammatory, antidiabetic, and antitumor agents. They also assist in neuroprotection, hepatoprotection, and cardio-protection.[35,36] Chemically, they consist of 2 isoprene units formed by five carbons joined together head-to-tail. These biochemically active units are diphosphate esters, isopentyl diphosphate, and dimethylallyl diphosphate. Monoterpenes are further subdivided into acyclic, monocyclic, bicyclic, and iridoid glycosides.[37] These are mainly found as active ingredients in essential oils and fixed oils from plants and related sources.[35] Besides their biological activities, they are also used as fragrant sources for making cosmetics and perfumes due to their strong aroma and odor.[38] Some of the most common monoterpenes employed for anticancer activity are described below.

2.2.1 **Carvacrol.** It is a monoterpene polyphenol mainly obtained from the Lamiaceae family's essential oils and is chemically 5-isopropyl-2-methyl phenol.[39] It is widely used in different biological applications to prevent the proliferation of chemotherapy-resistant cells such as human ovarian adenocarcinoma cells and tumor cells.[40,41] Compared to single drug-loaded nanoparticles, human serum albumin particles, when loaded with carvacrol and a chemotherapy agent, yield better activity in treating gastric cancer *in vitro*.[42] It was found to induce cell death by directly activating the mitochondrial pathway. They inhibited reactive oxygen species (ROS) generation and deoxyribonucleic acid (DNA) damage caused by cell proliferation. Proteins that regulate apoptosis and the antiproliferative effect of carvacrol are Bax, B-cell leukemia/lymphoma 2 protein (BCl_2), cysteine-aspartic proteases) (caspase)-3, and caspase-9.[43] In addition, they exhibit glutathione (GSH) reducing effects on cells.[34]

2.2.2 **Geraniol.** It is an acyclic isoprenoid monoterpene commonly present in the natural oils of fragrant herbal plants. It inhibits cell proliferation and causes apoptosis induction and cell cycle arrest in the gastric cancer cell line. The major factors involved are ROS production through mitochondria and downregulation of the mitogen-activated protein kinase (MAPK) pathway, mainly engaged in migration, survival, differentiation, and metabolism.[44] Furthermore, there is a drastic downfall in the phosphorylation of essential MAPK signaling molecules, including p38, Jun N-terminal kinases (JNK), and extracellular signal-regulated kinase (ERK). Proapoptotic proteins such as Bax and caspase-3, -8, and -9 are unregulated, whereas there is a reduction in Bcl_2 expression after treatment with geraniol which induces apoptosis.[44]

2.2.3 **D-carvone.** It is a cyclic and natural dietary monoterpene commonly present in the vital oils of certain plants, which are aromatic and medicinal in nature, including caraway, dill weeds, *etc.*[45]. Apart from other biological properties, it is found to prevent lung injury in mice,[46] lowers the lipid content in the blood, and can be used to cure diarrhea, acidity, and other gastric ailments.[47] Carvone is responsible for inhibiting cell proliferation and induction of apoptosis by regulating ROS production. It decreases the phosphorylation of Janus kinase/signal transducer and activator of transcription (JAK/STAT 3) molecules involved in cell growth and proliferation in a dose-dependent manner.[46]

2.2.4 Paeoniflorin. It is a monoterpene glycoside of the Paeoniaceae family and is extracted from the roots of *P. lactiflora* (*Paeonia lactiflora*). It exhibits hepatoprotective, immunomodulatory, and antitumor activity. It inhibits the proliferation of gastric cells and induces apoptosis. It mediates the upregulation of Bcl-2 by blocking the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathway in a dose and time-dependent manner. It also prevents the phosphorylation of IκBa (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha), which further inhibits the NF-κB activity and NF-κB p65 expression. It is also found to upregulate the expression of minR-124 and blocks the phosphoinositide-3-kinase-protein kinase B/Akt (PI3k/Akt) and STAT3 pathway.[48] It inhibits the Notch 1 pathway.[49]

2.3 Diterpenes

They belong to a naturally occurring class of chemical constituents comprising four isoprene units combined, thus having a core skeleton of 20 carbons. They are derivatives of geranyl pyrophosphate[50] and are produced by plants, animals, and fungi *via* 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase pathway 3.[51] They exhibit several biological activities such as antioxidation, antimicrobial, anti-inflammatory, anticarcinogenic and neurobiological.[52] Compared with monoterpenes and sesquiterpenes, they are fewer in number and less volatile.[53] Some of the significant diterpenes are discussed below.

2.3.1 Andrographolide. It is a diterpene lactone mainly obtained from *A. paniculate* (*Andrographis paniculate*), a traditional Chinese herbal plant belonging to the Acanthaceae family that reduces swelling and is used as a blood-cooling agent and a detoxifier for the body.[54] As a treatment for gastric cancer, it decreases the cell survival ratio of SGC7901 gastric cancer cells in a dose-dependent manner. The number of cells arrested in the G1/M phase increases with an increased dose, while the cell cycle is blocked in the G2/M2 phase. When used in an appropriate amount, andrographolide inhibits cell invasion, migration, and proliferation. It induces apoptosis, with possible mechanisms including the enhanced expression of Timp-1/2, cyclin B1, Bax, Bik and *p*-Cdc2 and decreased expression of MMP-2/9 and Bcl-2.[55] It also inhibits NF-κB binding to DNA.[56]

2.3.2 Sageone. It is an abietane diterpenoid commonly obtained from the crude extract of *R. officinalis (Rosmarinus officinalis)*. It causes cell death in gastric cancer cell line SNU-1 cells in a programmed manner. These cells are usually resistant to cisplatin, but when given synergistically along with sageone, they show the increased cytotoxic effect of cisplatin which was verified by the calculation of the combination index. Sageone decreases the level of Akt expression in contrast to cisplatin which increases it. It also increases the cleaved caspase-3 and -9 and poly (ADP-ribose) polymerase (PARP) when administered with cisplatin.[57,58] The indication is that caspase plays an essential role in the induction, transduction, and amplification of apoptosis.[59]

2.3.3 Carnosic acid. It is a polyphenolic abietane diterpene isolated from *R. officinalis* that exhibits several pharmacological activities. It is used for different stomach ailments, such as gastric lesions, which increase the level of reduced glutathione and prostaglandin-E2 to protect the stomach from lesions induced by lipid peroxidation inhibition.[60] It exhibits anti-gastric cancer activity by inhibiting the proliferation and survival of cells in a dose-dependent manner. It enhances the cleavage of the well-known apoptotic marker PARP and decreases survival expression. Furthermore, it inhibits the activation/phosphorylation of Akt and the mammalian target of rapamycin (mTOR) signaling pathways.[61]

2.4 Triterpenes

They consist of 6 isoprene units having 30 carbons in which squalene epoxide units are arranged in the chair-chair-chair-boat confirmation after the condensation process.[62] The primary sources of triterpenes are plants and fungi.[63] These are the main plant membrane structure constituents responsible for stabilizing the phospholipid bilayer in the cell membrane.[62] They perform numerous biological functions ranging from antioxidant, antiviral, antibacterial, anti-fungal, anti-inflammatory, and anticancerous activities, influencing several signaling pathways in cancer treatment.[63] Pentacyclic terpenes are plants' primary and secondary metabolites from their leaves, roots, stem barks, and fruits.[64] The four triterpenes commonly used in gastric treatment are described below.

2.4.1 Celastrol. It is a quinone methide triterpene, also known as tripterine, found in the extract of *T. wilfordii Hook. F* (*Tripterygium wilfordii Hook F*). It has been found to inhibit cancer cell proliferation and induce apoptosis. When tested on MKN45 gastric cancer cells, celastrol inhibits cell proliferation, migration, and invasion. It further plays a role in inactivating the PTEN/PI3K/Akt and nuclear factor κB signaling pathway by causing the downregulation of miR-21.[65] It decreases the expression of the phosphorylated forms of m-TOR and S6K and induces autophagy.[66] Also, it binds to an antioxidant enzyme, peroxiredoxin-2, which increases ROS at the cellular level and causes ROS-dependent endoplasmic reticulum stress and dysfunctioned mitochondria. It inhibits enzyme activity at the cellular and molecular level.[67] It inhibits TNF (tumor necrosis factor) induced tumor cell invasion and acts as an inhibitor of heat and shock response activation and as a proteasome inhibitor (it inhibits the chymotrypsin-like activity of a purified 20S proteasome and cancer cell 26S proteasome).[68]

2.4.2 Euphol. It is a euphane-type tetracyclic triterpene alcohol obtained from the sap or latex of *E. tirucalli* (*Euphorbia tirucalli*). It is utilized for its effects on rheumatism, toothache, and neuralgia and as an anticancer drug. It increases the expression of BAX, a pro-apoptotic protein and decreases the expression of Bcl-2, a prosurvival protein. Furthermore, it causes the dysfunction of mitochondria by activating caspase-3. The decreases in the cyclin-B1 level and increase in $p27^{kip1}$ are responsible for its antiproliferative activity. Finally, euphol also inhibits the activation of the extracellular signal-regulated kinase $\frac{1}{2}$ (ERK$\frac{1}{2}$) pathway.[69]

2.4.3 Glycyrrhizic acid. It is a natural triterpene isolated from the roots of the Chinese herb Licorice and found to exhibit anticancer effects against certain cancers. It assists in detoxification and bronchodilation and treats viral hepatitis.[70] It shows both dose and time-dependent inhibitory effects against gastric cancer cell lines. It downregulates the expression of proteins linked with the G1 phase, such as D1, D2, D3, E1, and E2, and causes G1/S phase arrest. It also increases the expression of Bax, cleaved PARP, and pro-caspase-3, -8, and -9, decreases that of Bcl-2, survivin, and p65, and further causes downregulation in phosphorylation of the PI3K/Akt pathway.[70]

2.4.4 Betulinic acid. It is a pentacyclic triterpene with a lupine-like structure obtained from several plants, such as acuminatissima leaves, wild jujube seeds, and white birch bark. It significantly affects gastric cells in both time and concentration-dependent ways. It induces cell death and inhibits the invasion and migration of gastric cancer cells by impairment of epithelial–mesenchymal transition progression.[71] It also blocks the ERK/MEK signaling pathway by decreasing the expression of the phosphorylated proteins ERK and mitogen activated protein kinase (MEK).[72]

2.5 Sesquiterpenes

Many sesquiterpene compounds are found naturally and play a significant role in biological activities and other human uses. They are very diverse and have two distinct characteristics – the presence of a 15 carbon skeleton that makes up the backbone and the arrangement of different functional groups and substituents in layers on the structural scaffolds. The constituents are arranged in diverse regiospecific and stereo-specific manners.[73] They can be monocyclic, bicyclic, or tricyclic. When compared with terpenes, they are less volatile. They have a more pungent odor and show anti-inflammatory and antibacterial properties.[74,75] After oxidation, sesquiterpenes get converted into sesquiterpenols.[76] The α-methylene-γ-lactone group (αMγL) of sesquiterpenes is responsible for anticarcinogenic and anti-inflammatory activity, whereas helenalin causes anti-inflammatory effects only and parthenolide accounts for antitumor activity. Furthermore, sesquiterpene lactone artemisinin exerts antimicrobial effects.[77] A few of the common sesquiterpenes for gastric cancer are described below.

2.5.1 Zerumbone. It is a cyclic sesquiterpene whose biological effect is due to unsaturated carbonyl groups. It is obtained from subtropical ginger and has significantly less toxicity. It inhibits the growth of gastric cells and causes apoptosis in a dose-dependent manner. Furthermore, it decreases the expression levels of Cyp-A, Bcl-2, and mitochondria-mediated pathways, increases the expression level of Bax, releases cytochrome-C, and activates caspase-3.[78] Furthermore, it reduces the expression of vascular endothelial growth factor (VEGF) and NF-κB.[79]

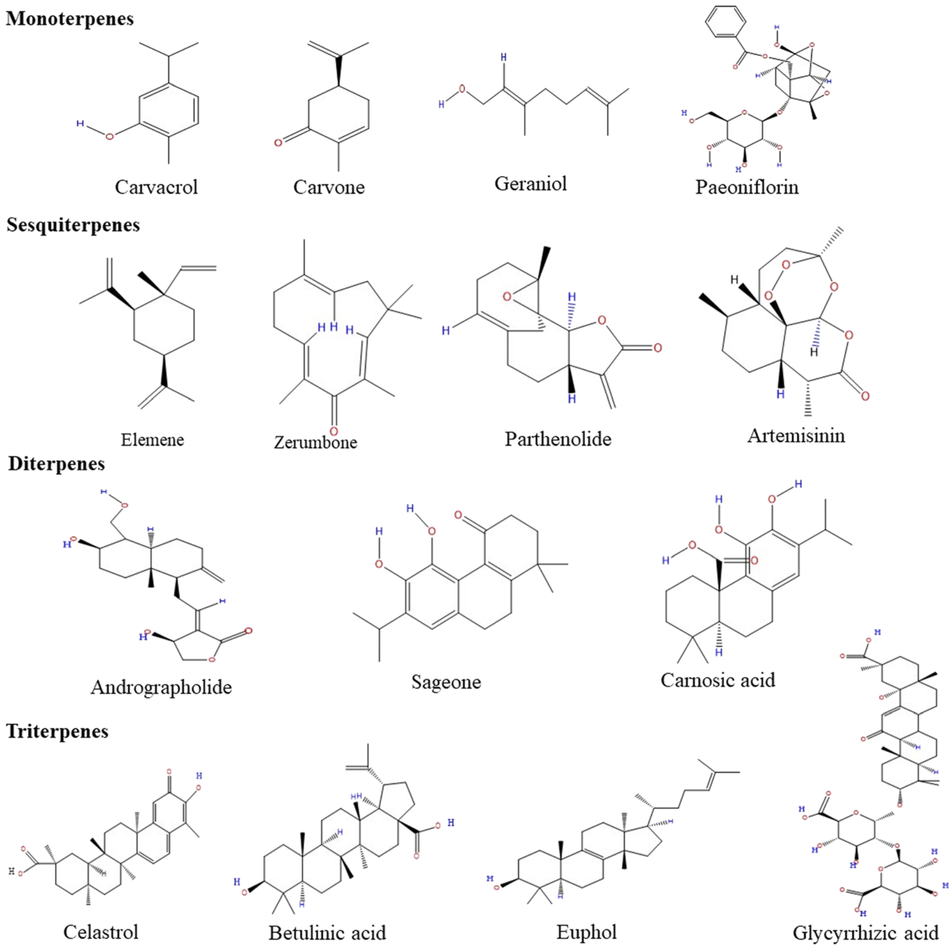

Fig. 1 The chemical structures of different monoterpenes, sesquiterpenes, diterpenes and triterpenes.

2.5.2 Elemene. It is a sesquiterpenoid obtained from the extract of *Rhizoma curcumae*, a part of traditional Chinese medicine, and has enormous potential to cure cancer and malignant tumors with essential oils. It is more clinically effective, safe, and less toxic than other cancer drugs. It inhibits the proliferation of gastric cells and exhibits a synergistic effect when administered along with PD98059. It indicates enhanced apoptosis in cells when given in a concentration-dependent manner. Elemene decreases the mRNA-expression level of Bcl-2 and increases the expression of the *p*-ERK1/2 protein along with BAX-mRNA.[80,81]

2.5.3 Parthenolide. It is a sesquiterpene lactone and is a medicinal compound obtained from *Parthenium*, which was initially used to treat migraines, epidermal infections, and rheumatism.[82] When tested on gastric cancer cell lines SGC7901, it inhibits cell growth, enhances the apoptotic rate, and sensitizes the cells to DPP. Parthenolide further acts by decreasing the expression of Bcl2, mitochondrial potential, and

Table 1 List of terpenes, their biological properties, source, and dose against cancer

Compounds	Biological properties	Source	Cell line	Dose
Carvacrol	Anti-microbial, antitumor, anti-inflammatory, anti-mutagenic, analgesic, and antiparasitic[88]	*Thymus vulgaris*, *Origanum vulgare*, *Lepidium flavum*, and *Citrus*[89]	AGS[34,43]	0–600 μmol l^{-1} (ref. 43)
Geraniol	Antitumor Anti-inflammatory	Lemon, geranium	AGS[44,90]	5–35 μM ml^{-1} (ref. 44)
d-Carvone	Antimicrobial, antioxidant, anti-inflammatory, and anti-cancer[91]	Caraway and dill weeds	AGS[46]	5–35 μM (ref. 46)
Paeoniflorin	Antitumor	*P. lactiflora*	SGC-7901, MGC-803,[48] HepG2 (liver cancer), SMMC-7721 (liver cancer),[92] SGC-7901 (gastric adenocarcinoma cell),[93] and MCF-7 (breast cancer cell)[94]	80–324 μg ml^{-1} (ref. 93)
Elemene	Anticancer	*Rhizoma curcumae*[80]	BGC-823 (ref. 80)	0.02–0.16 mg ml^{-1} (ref. 80)
Zerumbone	Anticancer and anti-angiogenic	Ginger[78]	SGC-7901 (ref. 78)	0.1–50 μM ml^{-1} (ref. 78)
Parthenolide	Antitumor	Feverfew (*Tanacetum parthenium L. Schulz Bip.*)[95]	SGC7901,[83] colon carcinoma cells, lung cancer[85]	5–200 μmol l^{-1} (ref. 83)
Artemisinin	Antitumor, antimicrobial, antioxidant	*Artemisia annua*[96]	AGS and MKN74[87] brain cancer, breast cancer, cervical, colorectal, gastric, lung, and ovarian cancer[97]	0–5 μM (ref. 87)
Andrographolide	Anticancer Anti-inflammatory	*Andrographis paniculata*	SGC 7901 cells[55], Jurkat, PC-3, HepG2, and colon 205 tumor cells, and normal peripheral blood mononuclear cells (PBMCs)[98]	5–40 μg ml^{-1} (ref. 55)
Sageone	Anticancer	*Rosmarinus officinalis*	Gastric adenocarcinoma cell lines AGS, SNU-1, and SNU-16 (ref. 59)	6.25–100 μM (ref. 58)
Carnosic acid	Antitumor	*Rosmarinus officinalis*	AGS and MKN-45 cells[61]	6.25–100 μg ml^{-1} (ref. 61)
Celastrol	Anti-inflammatory and antitumor	*Tripterygium wilfordii* (Thunder god Vine), *Celastrus orbiculatus*, *Celastrus aculeatus*, *Celastrus reglii*, and *Celastrus scandens*[99]	MKN45 (ref. 65) melanoma tumor cells[68]	0–20 μM (ref. 65)
Euphol	Antiviral, anti-inflammatory, and anti-cancer[69]	*Euphorbia tirucalli*[69]	CS12 (ref. 69)	2–60 μg ml^{-1} (ref. 69)
Glycyrrhizic acid	Immunomodulatory Antitumor	Licorice *Glycyrrhiza glabra L.*[100]	MGC-803, BGC-823, SGC-7901 (ref. 70) KATO III, HL 60, DU-145 & LNCaP[101,102]	0–4 mg ml^{-1} (ref. 70)
Betulinic acid	Antiviral, antibacterial, antimalarial, anti-inflammatory, and anticancerous[71]	Jujubee seeds and white birch bark[71]	SNU-16 and NCI–N87 (ref. 71)	0–80 μM (ref. 71)

NF-κB while upregulating caspase-8 and caspase-3 expression. It also enhances the release of cytochrome C from mitochondria and upregulates Bax, Bid, and tBid expression.[83] Thus, it increases the expression of the proapoptotic pathway, whereas it decreases the expression of the prosurvival and drug resistance pathways.[84,85]

2.5.4 Artemisinin. It is a sesquiterpene that is naturally obtained from *A. anuua* (*Artemisia annua*) or sweet wood and is commonly used as an antimalarial drug and exhibits an antiproliferative effect.[86] It also triggers cell cycle arrest in prostate cancer cells. When tested on gastric cancer cell lines AGS and MKN74 cells, artemisinin inhibits the growth and modulates the expression of cell cycle regulators. It also induces two negative cell cycle regulators, namely $p27^{kip1}$ and $p21^{kip1}$, and upregulates the expression of p53, which is essential for cell apoptosis and metastasis. In addition, it affects specific signaling pathways, ERK1/2, p38, and JNK, at the molecular level.[87] It decreases proliferation, increases levels of oxidative stress, induces apoptosis, and inhibits angiogenesis.

The structures of monoterpenes, sesquiterpenes, diterpenes, and triterpenes are given in Fig. 1. The details of different terpenes, their properties, sources, and modes of action against cancers are shown in Table 1.

3. Nanotechnology and herbal formulations

With conventional therapeutic and diagnostic tools for cancer, there is an increase in systemic toxicities and refractoriness. Due to this, various other strategies are used to enhance diagnostic abilities and combat disease severity.[103] Among these, nanotechnology has gained attraction due to its many inherent advantages. Various nanotechnology-based devices are being developed for their beneficial roles in detection, drug delivery, gene & targeted therapy, biomarker mapping, bioimaging, early diagnosis, and rapid testing.[103–105] Recent advancements in nanotechnology, especially in the synthesis of nanoparticles, have helped address some issues that were otherwise not possible, such as low target specificity, and improved disease diagnostic ability in terms of sensitivity, quality, speed, early detection, biocompatibility, stability, and effectiveness of drugs.[106]

Nanoparticles can be synthesized by various means, such as physical, chemical, and green methods. Chemical methods comprise high energy consumption, high cost, low yield, and environmental degradation through harsh reducing agents.[107] Physical techniques are also not preferred since they involve high cost, high pressure & high temperature and are not amenable to control the size & shape of nanoparticles.[108] However, because of the use of toxic chemicals in synthesizing nanoparticles, greener methods are preferred in which the particles are synthesized by following a redox reaction in which the reduction of metal ions to stabilize nanoparticles is carried out by using natural extracts or components of an organism. Recently, research on green synthesized nanoparticles has increased exponentially worldwide due to the widespread use of different plant species, isolated compounds, and extracts. Furthermore, green synthesized nanoparticles have low cost, environment-friendly behavior, energy efficiency, easy synthesis, better bio-activities, high catalytic activities, and low toxicity. For instance, a large number of green nanoparticles have been synthesised using extracts of different plants having terpenes as secondary metabolites. Their mode of action on different gastric cancer cell lines and *H. pylori* has been investigated.[109–114] For example, leaf extract of *Artemisia turcomanica* upregulates BAX mRNA expression and inhibits Bcl2 expression and increases the number of early and late apoptotic cells,[109] Artemisia ciniformis up-regulates pro-apoptotic genes, caspase-3, caspase-9, and Bax, down-regulates the Bcl2 gene, inhibits the expression of cyclin D1 and MMP2 genes and causes the arrest of cancer cells in the G0/G1 phase,[110] *C. monogyna* induces apoptosis and ROS generation,[111] *Cardiospermum halicacabum* induces apoptosis *via* inhibiting antiapoptotic proteins as well as proapoptotic proteins,[112] *Cassia fistula* leaf extract causes bacterial cytoskeleton disruption and DNA damage in *H. pylori*,[113] and *Vitex negundo* ethanolic extract augments expression of caspase-3, caspase-9, Bid and Bax and reduces expression of Bcl-XL.[114] Similarly, quantum clusters and quantum dots are being synthesized using different proteins, natural polymers, *etc.* For instance, insulin-protected quantum clusters are made using other metal ions, such as nickel, zinc, *etc.*, for their role in developing biomarkers using the green synthesis method.[115,116]

Similarly, biomarkers can be developed to detect cancer more precisely & efficiently.[103,117] Coal-GO (graphene oxide) exhibits higher interaction with single-stranded DNA aptamers, resulting in chemiluminescence resonance energy transfer-based biosensors with higher sensitivity.[118] Also, apigenin, a natural flavone, exhibits synergistic anticancer activity with curcumin after binding with tubulin at different sites.[119] Ginger, which has been used since time immemorial as a traditional medicine, shows antiproliferative activity when used as an aqueous extract by disrupting the microtubule network of cancer cells.[120] A bacterioboat-based drug carrier consisting of surface-encapsulated mesoporous nanoparticles on *L. reuteri* was developed for suitable oral administration of drugs.[121]

Nanomaterials also offer an advantage in minimizing the limitations of various imaging techniques, such as MRI (magnetic resonance imaging), X-ray, CT-scan (computed tomography scan), and ultrasound that are commonly deployed to enhance the diagnostic accuracy and progression of the disease. These techniques can only examine the alterations on the surface of the tissue, which is also relatively late in the progression of the disease. In addition, when used with imaging contrast agents, such as small molecules with a fast metabolism, unwanted toxic side effects are commonly experienced. By comparison, nanomaterials can be synthesized to act as powerful contrast agents in all imaging techniques due to their ability to show less toxicity and more permeability in tissues. For example, quantum dots are widely used for specific cellular imaging, and iron oxide particles are used for tumor imaging.[20,122–124] Following this, the development of nanoscale range drug delivery tools using nanotechnology can be used for targeting cancer tissue more precisely and with little or no side effects. Nanomaterials are also widely used in drug delivery due to their biological nature, ability to cross cell barriers easily, and active & passive targeting nature.[103,125,126] Using these, various novel methods for drug delivery are being developed that have been proven clinically effective. For instance, paclitaxel, incorporated with polymeric mPEG-PLA micelles, is used for treating metastatic breast cancer chemotherapeutically.[20,127]

Furthermore, anticancer therapies are often considered superior only when the therapeutic agent can reach the target site without causing side effects. With nanoparticles used as carriers, this can be relatively easily achieved by chemically modifying carrier surfaces. For example, incorporating PEG (polyethylene glycol) or polyethylene oxide at the surface of nanoparticles enhances tumor targeting ability because PEG prevents nanoparticle detection as an antigen by the body's immune system, thus making it easy to circulate in the bloodstream. Another example, Abraxane, a nanoparticle formulation consisting of albumin-stabilized paclitaxel, is FDA (Food and Drug Administration) approved for treating breast cancer.[20,128]

In a nutshell, different nano-formulations utilized for curing various cancers can be exploited for treating one of the deadliest diseases, gastric cancer. Several preclinical studies prove that synthetic and naturally occurring terpenes have therapeutic and chemopreventive effects against cancer. They act by exerting their effects on various developmental stages of the tumor *via* inhibiting initiation and promotion of carcinogenesis, inducing tumor cell differentiation and apoptosis, and suppressing tumor angiogenesis, invasion and metastasis by regulating various growth factors, transcription factors, and intracellular signaling pathways.[129–131] Thus, nanotechnology can be employed for developing new formulations using different herbal secondary metabolites for treating gastric cancer. Several nano-formulations have been made using plant extracts, with metal ions that exhibit antioxidant, anti-cancerous, anti-inflammatory, antiviral, and antibacterial properties.[132–135] SEM (scanning electron microscope) and TEM (transmission electron microscope) images of some of the green synthesized nanoparticles are given in Fig. 2. The various applications of green synthesized nanoparticles are given in Fig. 3.

3.1 FDA-approved drugs for gastric cancer

FDA is a federal agency of the Department of Health and Human Services. It protects public health by assuring the safety and efficacy of human and veterinary drugs, medical devices, food supplies, and biological products. Since the last 50 years, more than 100 anticancer drugs have been approved for various cancers by the FDA. The approval of drugs is based on 3 distinct parameters: overall survival or patient related outcomes, progression-free survival involving the time until cancer worsens or occurs again, and the response rate which involves the percentage of people experiencing tumor shrinkage. The drugs are divided into two categories depending upon their mode of action: cytotoxic or targeted agents. Cytotoxic drugs target the components of the mitotic or DNA replication pathways thus killing rapidly dividing cells. They include mainly alkylating agents, topoisomerase inhibitors or anti-microtubule agents. On the other side the targeted agents interact with the molecular targets involved in the pathways

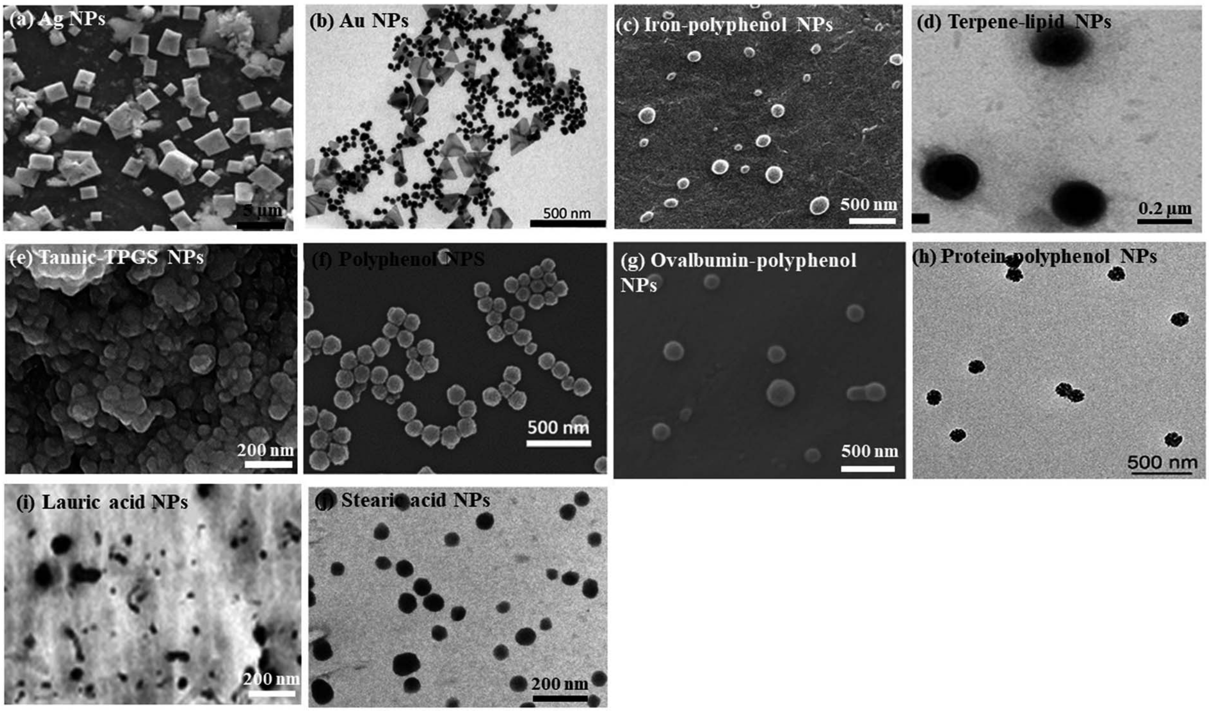

Fig. 2 SEM/TEM images of some of the green nanoparticles synthesized using terpenes and other polyphenols. (a) Ag nanoparticles. (b) Au nanoparticles. (c) Iron-polyphenol nanoparticles. (d) Terpene-lipid nanoparticles. (e) Tannic-TPGS nanoparticles. (f) Polyphenol nanoparticles. (g) Ovalbumin-polyphenol nanoparticles. (h) Protein-polyphenol nanoparticles. (i) Lauric acid nanoparticles. (j) Stearic acid nanoparticles.

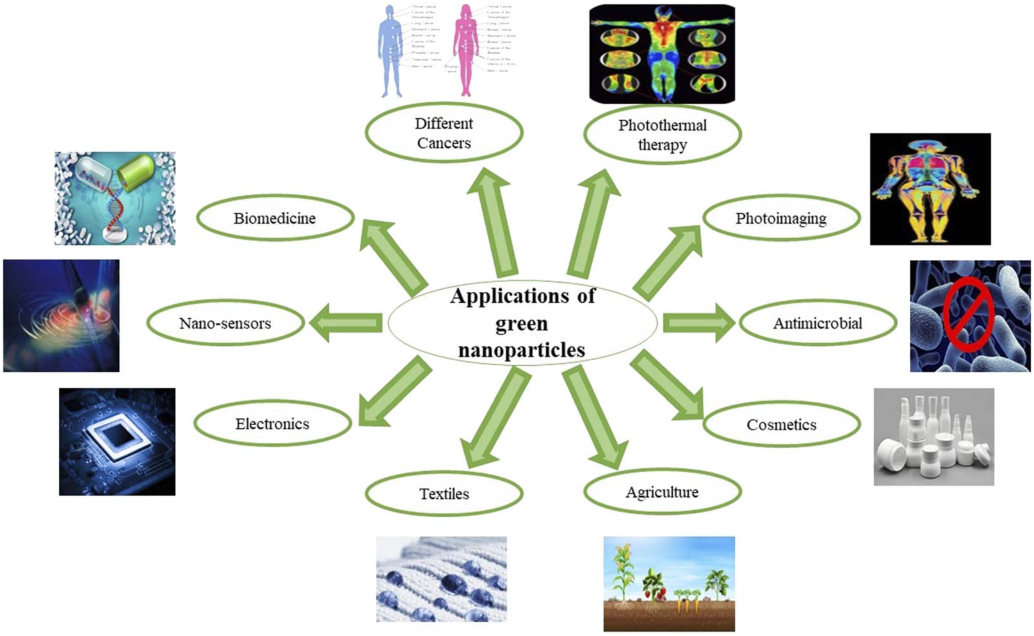

Fig. 3 The significant fields in which green synthesized nano-formulations have been used for the past few years.

related to growth, progression and spread of cancer, eventually blocking the growth and spread of cancer. This category comprises mainly of signal transduction inhibitors, apoptosis inducers, gene expression modulators, monoclonal antibodies, and hormone therapies.[136] For treatment of gastric cancer, some of the mainly consumed anti-gastric cancer drugs are listed in ESI Table 1,† which includes their structure, mechanisms of action, and side effects. A brief description of the first few drugs listed in the table is discussed next. Everolimus is a mTOR inhibitor, which results in G0/G1 arrest by preventing the mTOR mediated phosphorylation of p70S6K and 4E-BP1.[137] It also decreases the proliferation and attenuates the production of HIF-1α and VEGF in gastric cancer cells *in vitro*. Ramucirumab, on the other hand, is a human monoclonal antibody IgG1, which acts by targeting vascular endothelial growth factor receptor-2 (VEGFR-2). It prevents VEGF ligand binding to VEGFR-2 and receptor-mediated pathway activation in the case of endothelial cells. Furthermore, it also results in macrophage inhibition which causes decreased tumor immune infiltration and cytokine-chemokine release which results in decreased tumor growth and proliferation. It is the only FDA approved antiangiogenic agent for gastric or gastroesophageal junction adenocarcinoma.[138,139] Another FDA approved drug, trastuzumab, is also a humanized monoclonal antibody which is directed against epidermal growth factor receptor 2 (HER2). It treats multiple oncologic conditions, metastatic gastric cancer being one of them. It acts by binding to the extracellular domain of HER2 and follows various mechanisms including downregulation of the DNA repair pathway and angiogenesis, abrogation of oncogenic cellular signaling, activation of antibody dependent cell-mediated cytotoxicity, and inhibition of extracellular HER2 domain cleavage to trigger tumor-suppressive action.[140] For the FDA-approved drugs, the reader is referred to ESI Table 1.†

4. Concluding remarks and directions for future research

Gastric cancer cases are reported worldwide, with maximum prevalence in Asia and Latin America; the rate is also high from northern to central America, Europe, and central Africa. But even countries with good economies and advanced medical facilities have not been able to reduce the death rate considerably. The 5-year survival rate in the USA for gastric cancer is 31%, and for the European nations it is around 26%. The situation is similar or worse in countries with weak economies and poor hygiene. Therefore, there is an urgent need and high demand for the development of abundant, effective, and economically favorable medicines. Furthermore, available chemotherapy, including 5-fluorouracil, capecitabine, carboplatin, cisplatin, docetaxel, epirubicin, oxaliplatin, *etc.*, has considerable side effects such as anemia, shortness of breath, nausea, diarrhea, fatigue, loss of appetite, hair loss, *etc.*, which compromise the quality of life of the patient. Therefore, more research is needed to develop suitable treatments/drugs with fewer side effects.

Since almost 89% of gastric cancer directly relates to *H. pylori* infection, the most crucial step in gastric cancer management is to control the infectivity. Plants such as *Hedyotis diffusa Willd*, *Aloe vera*, *Rhizophora mangle*, *Astragalus membranaceus*, *etc.*, are effective against the pathogen due to the presence of phenolics, terpenes, alkaloids, and polyketides in them. Many of those plants grow in the tropical, subtropical, temperate, and Mediterranean regions of the world and are native to a particular geographical location such as India, China, Japan, South Africa, Iraq, Iran, Vietnam, the USA, and other European countries and show excellent anti-*H. pylori* activity. Extensive research is needed to invent, purify, characterize, and formulate safer drugs, including natural products. Attention should also be given to the composition, stability, and pharmaceutical efficiency of those formulations as the concentration and the stability of the lead compounds may greatly vary based on many factors, including soil composition, pH, macro and micronutrient content, humidity, porosity, weather, availability of sunlight, *etc.* In this regard advancement of nanotechnology may play a critical role in maintaining the quality and efficacy of herbal formulations. Many metallic nanoparticles, including silver, gold, selenium, zinc oxide, *etc.*, have anti-cancer properties. Enhanced uptake of nanoparticles by cancer cells has been reported for many cancer lines, including MCF-7 (human breast carcinoma cell line),[141] Hep G2 (human liver cancer cell line),[142] and AGS (human gastric carcinoma cell line).[110] Nanoparticles and these natural compounds may show synergistic anticancer activity by generating various stresses, including oxidative damage, DNA damage, and mitochondrial dysfunctions.

Furthermore, many nanoparticles also show anti *H. pylori* activity. In addition, due to the high surface area to volume ratio, nanoparticles can interact with and stabilize bioactive polyphenols on their surfaces, enabling the delivery of a large quantity of the drugs at the target site. Cancer cell specific delivery of herbal medicines will make them safer and side effect free. Furthermore, polyphenolic surface-protected ferromagnetic nanoparticles will allow the detection and imaging of the cancer tissue using MRI imaging techniques and help develop an effective therapeutic approach using hyperthermia.

In conclusion, medicinal plants show promise as potential candidates for cancer treatment due to their beneficial properties. Knowledge of active secondary metabolites from extracts of different plant parts having anti-cancerous activities and their mode of action against critical targets paves the way for further research. The current information on various herbs and their modes of action against different diseases can be further exploited to develop more efficient and less harmful drugs. At a minimum, when used with conventional treatments, they can increase the effectiveness of these treatments in fighting cancer. Moreover, isolating active compounds and finding their chemical structure further enables molecular and pharmacological comparison with the currently used chemicals and pharmaceutical products. In the case of *H. pylori*, which has become resistant to conventional antibiotics, green nano-formulations with high biocompatibility and bactericidal potency can be utilized as a replacement. We conclude this review article by outlining directions for future research on NT (nanotechnology)-enabled herbal formulations for treating cancer, particularly gastric cancer.

We believe that herbal formulations using the unique properties of nanomaterials offer a potentially winning proposition. It is our hope that this review article will spur interest among interdisciplinary teams of researchers in developing safer and more effective treatments for gastric cancer.

Conflicts of interest

The authors declare no conflict of interest.

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