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Review Article

Phytochemical and Anticancer Properties of *Cuscuta Reflexa*: A Therapeutic Approach for Future Insights

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ABSTRACT

Cuscuta reflexa, a parasitic plant, has been traditionally used in medicine for its diverse therapeutic properties. This review will focus on the phytochemical and anticancer potential of C. reflexa to emphasize its future applications in therapy. C. reflexa produced different bioactive compounds that include flavonoids, alkaloids, and phenolic acids with high anticancer properties. These phytochemicals have demonstrated encouraging outcomes in their preclinical trials, blocking the growth of cancer cells, triggering eventual cell death, and altering crucial pathways of signals. Antioxidant, anti-inflammatory and immunomodulatory effects of the plant extracts have also been established, which could lead to the anticancer activity of the plant. C. reflexa has not been exploited fully in modern medicine despite its potential and additional studies are required to help exploit its therapeutic potential. This review gives an overview of the phytochemical profile, anticancer pharmacology, and future trends in the research and development of C. reflexa. The list of current information on C. reflexa can possibly spur the further research of the topic, eventually resulting in the creation of the novel anticancer techniques.

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INTRODUCTION

Cuscuta reflexa, the giant dodder, is one of the most curious botanical specimens of nature a plant, which roots and leaves and made the parasite of herself. It is an outstanding species that belongs to the family Convolvulaceae, a family belonging to morning glory, a taxonomic family that has been confirmed and accepted by other significant botanical authorities across the world [1]. It is classified into the kingdom Plantae, division Tracheophyta (vascular plants), class Magnoliopsida, order Solanales and as the genus Cuscuta with about 100-170 species of dodder. The scientific name of the species was originally created by the botanist William Roxburgh in his book Plants of the Coromandel in 1799 and this remains the basis of its scientific description in modern times [2]. Leafless, perennial, and parasitic herb *Cuscuta reflexa* is given a golden-yellow hue, which has given it vernacular names like Swarnalata (golden vine) in India and Bangladesh. The plant morphology is typified with thick stem, fleshy and twining stems, which may proliferate in length and may be in form of mats of tangles around their hosts. *Cuscuta reflexa* does not synthesize or produce chlorophyll and so it cannot photosynthesize, which is unlike typical green vegetation and therefore wholly relies on its host plants to meet its nutritional needs [3]. It has a parasitic lifestyle, and wraps itself around the host plant in order to feed itself by utilising a set of special organs known as haustoria, modified roots that pierce the vascular tissue of the host to suck out water, nutrients, and carbohydrates. This adaptation will enable the plant to survive without the burden of working out its own food by photosynthesis, but this will come at a price of independence. The geographical spread of *Cuscuta reflexa* sp is also impressive in that it has a native area between the western part of the Asian continent including Afghanistan and the eastern part of the continent including Indo -China and even the Indonesia island of Java [4]. The plant has a high ecological flexibility within the extensive range of this territory and grows both in tropical and subtropics and sometimes expands to temperate areas. The Indian subcontinent is a notably important distribution centre, and the specimen has been reported to be common in the Bengal plains, the Western Ghats, Satara, Uttar Pradesh, Himachal Pradesh and Uttarakhand. It is also known in the Greater Himalayas, Nepal, Pakistan, Sri Lanka, Bangladesh, Myanmar, Thailand, Laos, Vietnam and southern China, including Tibet. Outside its native, the plant has been introduced to other areas, such as Mauritius, in the Indian Ocean, where it has developed populations [5]. Such a broad distribution is not only indicative of the ecological diversity of the plant, but also of its historical importance in the traditional medicine of various Asian cultures. *Cuscuta reflexa* has peculiar physical features, which are easy to identify. The plant gives thick, fleshy stems, and these are generally yellowish to orange colored with a reddish shading, and it may be of considerable length. In its large tree development, the vine can give garlands hanging down the canopy stretching up to 10 meters giving it a very beautiful physical appearance [6]. The absence of leaves is made up with the fact that the stem has the capacity to serve all the physiological roles needed. The flowers of the plant are small and bell-shaped, white and with yellow filaments, and form a delicate beauty to an otherwise vicious parasite during the flowering season. Such flowers later yield fruits and seeds and the species continues to exist. Interestingly, the *Cuscuta reflexa* which is a non-photosynthetic parasite still possesses hermaphroditic flowers, both with male and female reproductive structures, which enables the plant to reproduce even in the event of individual plants being in isolation Table 1.

Table 1: Major phytochemical constituents of *Cuscuta reflexa* and their anticancer properties

Chemical Class	Compound Name	Plant Part	Anticancer Mechanism
Phenolic Acids	Chlorogenic acid	Whole plant, stems	Antioxidant activity, apoptosis induction, anti-inflammatory effects, modulation of ROS production
	3,5-dicaffeoyl-quinic acid	Whole plant	Enhanced radical scavenging, metal chelation, anti-proliferative activity
	4,5-dicaffeoyl-quinic acid	Whole plant	Potent antioxidant activity, cytoprotective effects
Flavonoids	Quercetin	Stems, seeds	Apoptosis induction, caspase activation, PI3K/AKT pathway modulation, chemosensitization
	Kaempferol	Stems, seeds	Anti-proliferative effects, cell cycle arrest, anti-angiogenic activity
	Quercetin-3-O-glucoside (Isoquercitrin)	Stems	Improved water solubility, antioxidant activity, apoptosis induction
	Kaempferol-3-O-glucoside (Astragalin)	Stems	Anti-inflammatory effects, cytoprotective activity
Phytosterols	β-sitosterol	Stems, seeds	Apoptosis induction, caspase activation, PI3K/AKT modulation, minimal toxicity to normal cells
	Stigmasterol	Stems, seeds	Anti-inflammatory effects, anti-angiogenic properties, chemopreventive activity
	7β-methoxy-β-sitosterol 3-O-β-glucopyranoside	Stems	Novel steroidal glycoside, potential unique pharmacological properties
Terpenoids	α-amyrin	Whole plant	Anti-inflammatory activity, phospholipase A2 inhibition, hepatoprotective effects
	β-amyrin	Whole plant	Anti-inflammatory properties, COX inhibition, anticancer activity
	Lupeol	Whole plant	Multi-pathway targeting (NF-κB, PI3K/Akt, Wnt/β-catenin), chemopreventive and chemotherapeutic effects
	Oleanolic acid	Whole plant	Apoptosis induction, autophagy modulation, hepatoprotective and anti-inflammatory activities
Coumarins	Unidentified coumarin derivatives	Whole plant	Anti-inflammatory, antimicrobial, anticoagulant, potential anticancer through carbonic anhydrase inhibition
Novel Compounds	Cuscutaroside A	Whole plant	2H-pyran-2-one glucoside, potential cytotoxic and antimicrobial activities
	Cuscutaroside B	Whole plant	Novel glycosylated lactone, unique chemical scaffold for drug development

Phytochemical profile of *Cuscuta reflexa*

The phytochemical profile of *Cuscuta reflexa* demonstrates a great number of bioactive compounds that can explain the widespread therapeutic image of this plant. Extensive phytochemical studies carried out during several decades have confirmed that this parasitic plant produces an impressive number of species of secondary metabolites representing a wide range of chemical classes, each having its own unique structural features, and biological action [7]. The key classes of phytoconstituents detected in *Cuscuta reflexa* are phenolic compounds,

flavonoids, sterols, terpenoids, coumarins, and other specialized metabolites, and their distribution among the different parts of the plants is also widely different, the stems, the seeds, and the fruits all have distinct chemical profiles in the overall phytochemical repertoire of the plant. This compound richness indicates the evolutionary adaptation of the plant to its parasitic nature, in which the synthesis of a wide array of secondary metabolites has several ecological roles, such as protection against herbivores, competition with other parasites as well as influence the interaction with host plants [8-10]. These compounds have been isolated and characterized using advanced chromatographic methods in conjunction with spectroscopic ones allowing scientists not only to recognize the known compounds but also to discover new chemical components which are peculiar to this species. It is observed that the increased knowledge of the phytochemical profile of *Cuscuta reflexa* has given it a rational ground in its traditional applications, at the same time introducing new lines of therapeutic applications, especially in the context of cancer studies where most of these have shown favorable bioactivities Fig.1.

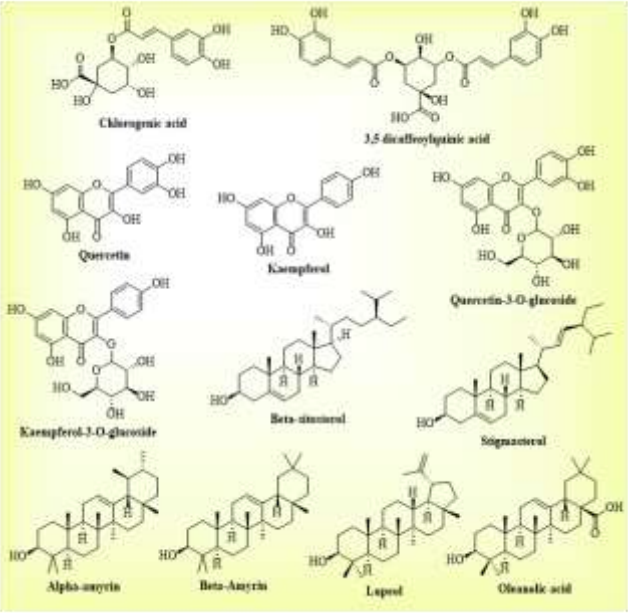


Fig.1: Phytochemical constituents of *Cuscuta reflexa*

Ethnopharmacological relevance and traditional uses

The ethnopharmacological importance of *Cuscuta reflexa* is so deeply rooted in the structure of traditional medical practices in Asia that the parasitic plant has been worshipped as a universal medicine since the antique times. Its application is recorded in some of the oldest traditions of continuous medicine in the world, or in Ayurveda, Unani, and other folk medicine systems around the Indian subcontinent, Bangladesh, China, and Thailand. The fact that the plant is being incorporated into these advanced medical networks testifies to the observational skills of traditional healers who through generations have discovered and elaborated the medicinal uses of this weird herb [11]. *Cuscuta reflexa* is mentioned in Ayurveda, the ancient Indian medicine, to treat ophthalmic diseases and heart ailments which are still a major health concern even in the present days. The Sanskrit word Aksavalli, meaning that which grows in the sky, is poetic, and indicates the ethereal nature of the plant, and alludes to its

celestial medicinal properties. The therapeutic uses of *Cuscuta reflexa* are so numerous that the types of *Cuscuta reflexa* used in all the formulations can only be referred to as the stem, seeds, fruits, and even the whole plant Fig.2.



Fig.2: Morphological character of *Cuscuta reflexa*

This holistic use is indicative of the notion that various plant parts can be the source of unique medicinal activity, which has been substantially proved in contemporary phytochemical studies. Traditionally used as a powder or juice the entire plant has been used in treating jaundice, a syndrome involving liver dysfunction, which suggests that there was early appreciation of the hepatoprotective effect of the plant [12]. In the same manner, the paste made of the plant is externally used to relieve rheumatism and gout, inflammatory ailments that bring a lot of pain and disability. The most available part of this leafless plant has been used to treat bilious disorders, constipation, flatulence and liver problems-digestive and hepatic disorders. The external uses of the stem are given in cases of lingering fever, pains in the body, and itch-like skin and also in the treatment of alopecia, or loss of hair. *Cuscuta reflexa* seeds take a number of special place in the traditional medicine, with their seeds being regarded with a number of therapeutic benefits in their use [13]. These are sedative, anthelmintic (removing parasitic worms), carminative (relieving flatulence), diuretic (promoting urine production), tonic (restoring and strengthening), diaphoretic (inducing sweating), and demulcent (soothing irritated tissues). This fabulous diversity of activities indicates the existence of several bioactive compounds which act through various physiological pathways. The seeds are specifically used in traditional Chinese medicine to treat hepatic and renal illnesses, and they are involved in the philosophical paradigm of remedying Yin and Yang deficiencies-a central paradigm of Chinese medical thought that tries to put back in place the vital energies within the body. The plant fruits are also used in medicine as they are regarded as the cure to fever and cough, the frequent illnesses which have threatened the curers of human history [14]. The list of the conditions that *Cuscuta reflexa* has traditionally been used to treat is quite extensive and covers migraines and headaches, constipation, chronic catarrh (inflammation of mucous membranes), epilepsy, prolonged fever, amnesia, and itching among

many others. This broad spectrum of therapy is indicative of the perceived treatment potential of the plant to treat disorders of the various body systems- nervous, digestive, respiratory, and integumentary. *Cuscuta reflexa* is the most popular in the rural areas of India where modern healthcare could be unavailable, and the plant was considered relatively safe, effective, and cheap. The plant is being integrated into many therapeutic formulations that are highly regarded in terms of effectiveness, which proves the timelessness of the traditional knowledge in modern healthcare practices [15]. The vernacular names used in various languages to refer to Cuscuta reflexa also testify to its cultural importance- it is called Akashbel in Urdu and Bengali, Amarabela in Hindi, Zarbut in Punjabi, Moodillathali in Malayalam, and Verillakothan in Tamil - all names reflecting the linguistic and cultural attitudes of the people to this wonderful plant. The interplay of ancient knowledge and contemporary science has developed an interesting case in favor of exploring the therapeutic effects of Cuscuta reflexa using strict pharmacological study. Long history of safe traditional use is a good starting point in the identification of possible therapeutic uses of the plant and the fact that it has been shown to be effective in treating various ailments is an indication that it has bioactive compounds that ought to be explored through scientific measurements [16]. One of the most promising research opportunities is that the plant has anticancer potential and this has increased pace as researchers attempt to comprehend the molecular pathways underlying traditional applications. Some initial scientific research has already started to prove the traditional knowledge in that *Cuscuta reflexa* contains antitumor, antioxidative, and anti-inflammatory properties that can be exploited to manage cancer. The relevance of these findings is that traditional medical knowledge must be retained and carefully analyzed since it could contain the solutions to some of the most difficult therapeutic issues that modern medicine is struggling with. The example of *Cuscuta reflexa*, whose traditional medicine has been turned into a modern, cutting-edge cancer treatment, is a good illustration of how ethnopharmacology could be used to shape the future of drug discovery and development and provide humanity with some hope of finding cures to one of the most dreadful illnesses.

Phenolic compounds and flavonoids

The phenolic compounds and flavonoids are some of the largest and most heavily investigated components of *Cuscuta reflexa* and are a large group of secondary metabolites that are known to have antioxidant properties and a variety of pharmacological properties. Hydroxycinnamic acids are one of the most significant subgroups in the phenolic profile of this plant, and chlorogenic acid turns out to be one of the most widespread and biologically significant phenols [17]. Chlorogenic acid is an ester of the caffeic acid and quinic acid that has got so much research attention because of its strong antioxidant, anti-inflammatory and anticancer value. In addition to this simple ester, there are also more complex derivatives of *Cuscuta reflexa*, such as the dicaffeoylquinic acids -that is, 3,5-dicaffeoyl-quinic acid and 4,5-dicaffeoyl-quinic acid- complex derivatives of caffeic acid in which the two molecules are esterified to the quinic acid backbone. The biological activities of these compounds are more active than those of the corresponding mono-caffeoyl compounds and this could be attributed to the fact that there are more phenolic hydroxyl groups to use in radical scavenging and metal chelation. These hydroxycinnamic acid derivatives, with their important levels of occurrence, are actively responsible to the overall antioxidant activity of the plant and offer a

mechanistic platform to its historical utilization in situations where oxidative stress is manifest [18].



Fig.3: Pharmacological activity of *Cuscuta reflexa*

The complement of flavonoid of *Cuscuta reflexa* is also superb with aglycone forms of flavonols and different glycosidic conjugates. The two main flavonol aglycones found in the plant are quercetin and kaempferol, and they are commonly known to be one of the most bioactive flavonoids present in the diet that has been demonstrated to have anticancer properties [19]. Specifically, quercetin has been widely studied as a stimulant of apoptosis of cancer cells, as well as an inhibitor of tumor growth and sensitizer of cancerous cells to standard chemotherapy, which is why its occurrence in *Cuscuta reflexa* is of particular interest to the anticancer potential of the plant. Nevertheless, they are majorly in their form as glycosides-conjugates in which sugar molecules are conjugated to the flavonoid backbone, their position usually being at the 3-position of the C -ring. These glycosidic structures, such as quercetin-3-O-glucoside (isoquercitrin) and kaempferol-3-O-glucoside (astragalin), have altered physicochemical characteristics relative to their aglycone equivalents, with their water solubility increased and their bioavailability profiles altered to alter their potential therapeutic effects in general. The glycosylation pattern also influences the human body in metabolic formation where they can be broken down to disclose the active aglycone formations at the site of actions through intestine enzymes. These synergistic reactions between these different phenolic compounds probably play a role in the total pharmacological character of *Cuscuta reflexa* extracts, which frequently show actions superior to those anticipated using individual separated compounds only [20].

Sterols and Terpenoids

The second important group of bioactive compounds with important therapeutic potential is the steroidal and terpenoid constituents of *Cuscuta reflexa*. The plant analogs of animal cholesterol, phytosterols, are highly expressed in this species with b-sitosterol and stigmasterol being the most prominent ones that have been identified by phytotranscriptomic studies on this plant species. Structurally related to cholesterol, these compounds have attracted significant scientific interest due to their cholesterol-lowering effect and more recently, their anticancer effect (induced apoptosis and control of the PI3K/AKT signaling pathway) and little toxicity in normal cells, a

favorable pharmacologic property in drugs used as anticancer agents. Stigmasterol supplements these actions with a range of its own biological actions such as anti-inflammatory and anti-angiogenic action that can be used in cancer prevention and treatment. In addition to these typical phytosterols, *Cuscuta reflexa* has provided new steroidal glycosides which are unique chemical compounds in the plant kingdom. 7b-methoxy-b-sitosterol 3-O-b-glucopyranoside is one of such compounds being a unique molecule with a methoxy group in position 7 of the sterol nucleus, which dramatically changes its chemical characteristics and, perhaps, its biologic functions. An example of this ability of *Cuscuta reflexa* is to synthesize structurally distinct secondary metabolites with potential novel pharmacological activity unavailable in more prototypical phytosterols [21-23].

The terpenoid fraction of *Cuscuta reflexa* also contributes to the phytochemical diversity of the plant with the presence of a-Amyrin and b-amyrin, two isomeric pentacyclic triterpenes, which are known to be anti-inflammatory, hepatoprotective and anticancerous. These are compounds that are present abundantly in the plant kingdom and found very useful in their property of regulating inflammation by inhibiting major enzymes like phospholipase A2 and cyclooxygenase, and subsequently suppressing the generation of pro-inflammatory mediators. Another pentacyclic triterpene, which has also been found in *Cuscuta reflexa*, is lupeol, which has proved to be a compound of considerable interest in cancer biology because of its ability to modulate several signaling pathways associated with cancer, such as NF-kB, PI3K/Akt, and Wnt/β-catenin. It has been shown to have chemopreventive and chemotherapeutic activity in a variety of preclinical cancer models, in which it inhibits tumor initiation, tumor promotion, and tumor metastasis. Oleanic acid is the final member of this terpenoid family, an established triterpenoid having hepatoprotective, anti-inflammatory, and anticancer effects. This substance demonstrates specific potential in cancer treatment in that it causes apoptosis and autophagy in cancer cell formations and also prevents damage to normal cells a two-faceted process that can perfectly fit the requirements of the contemporary oncology. The existence of these various terpenoids in *Cuscuta reflexa* is the basis of a large number of its traditional therapeutic and warrants further research on its anticancer potential [24].

Other notable compounds

In addition to the previously mentioned major classes of phytochemicals, *Cuscuta reflexa* expounds on some other interesting compounds which add up to the overall pharmacological effect and therapeutic versatility. Coumarins are a group of benzopyrone derivatives that is abundantly spread throughout the plant kingdom and which were also found in *Cuscuta reflexa* to further complicate its phytochemistry [25]. Associated with a sweet scented aromatic smell and with capacity to absorb the ultraviolet light, these compounds have varied biological functions, such as anticoagulant, anti-inflammatory, antimicrobial, and anticancer effects. The fact that the coumarins are available in the plant is of specific importance to the traditional application of the plant in treating inflammatory conditions, and also it could have played a role in its anticancer effects due to its ability to inhibit carbonic anhydrase and regulate oxidative stress. Some of these new structures include the recently discovered 2H-pyran-2-one glucosides, cuscutarosides A and B, which are previously unknown chemical structures. These derivatives of the comparatively rare 2H-pyran-2-one family include a six-member unsaturated lactone ring glycosylated with sugar moieties, a structural

theme related to a number of biological functions, comprising antimicrobial and cytotoxic actions [26]. Such unique compounds reinforce the idea that phytochemical research on medicinal plants is still worthwhile, as it is likely to provide new chemical scaffolds that can be used to develop drugs that would otherwise remain unknown through other methods. All these varied constituents, including common phytochemicals and species-specific novel compounds, have the potential to add up to the therapeutic potential of *Cuscuta reflexa* and serve as a rich chemical library to be studied in the future in pharmacological terms.

Medicinal plants have long served as a valuable source of bioactive compounds with significant therapeutic potential, particularly in the discovery of novel anticancer agents [27]. In recent decades, increasing scientific attention has focused on phytochemicals due to their multitarget mechanisms, reduced systemic toxicity, and ability to modulate complex cellular pathways involved in carcinogenesis [28-31]. Among medicinal plants, *Cuscuta reflexa*, a holoparasitic species widely used in traditional medicine, has emerged as a promising candidate owing to its rich phytochemical composition, including flavonoids, alkaloids, phenolic compounds, glycosides, and terpenoids [32]. These secondary metabolites are known to exhibit antioxidant, anti-inflammatory, cytotoxic, and apoptosis-inducing activities, which play crucial roles in cancer prevention and therapeutic intervention. Recent studies on plant-derived compounds emphasize their ability to regulate oxidative stress, inhibit tumor proliferation, and influence molecular signaling pathways associated with cancer progression [33]. Furthermore, extensive pharmacological investigations of medicinal plants and phytochemical-based therapeutics have demonstrated significant potential for integrating traditional botanical knowledge with modern drug discovery approaches [34-37]. Advances in phytochemical profiling, plant genomics, and green synthesis technologies have further expanded opportunities for developing novel plant-based therapeutics with enhanced bioavailability and targeted delivery [38]. Comprehensive reviews on medicinal plants and natural compounds highlight their therapeutic versatility and reinforce the importance of systematic pharmacological validation and mechanistic studies in anticancer research [39]. Despite increasing interest in phytomedicine, the anticancer mechanisms and therapeutic potential of *Cuscuta reflexa* remain insufficiently explored, indicating a significant research gap [40]. Therefore, detailed investigations integrating phytochemical analysis, molecular pharmacology, and translational research are essential to establish its efficacy and pave the way for future oncology-based therapeutic applications [41].

Anticancer properties

Systematic research on the topic of the anticancer potential of *Cuscuta reflexa* has been conducted by accumulating a substantial amount of in vitro research that supports in totality the convincing evidence of its cytotoxicity and antiproliferative properties against different cell types of cancers Table 2. These studies, using different extracts of solvents and isolated constituents of different sections of the plant have confirmed that *Cuscuta reflexa* has the ability to selectively suppress the growth and viability of the malignant cells and has a relatively lower toxicity to normal cells-a characteristic trait that defines a promising anticancer agent and a general cytotoxin [42]. The range of types of cancers that can be treated by *Cuscuta reflexa* is very wide; it includes lung cancer, breast cancer, cervical cancer, colon cancer, liver cancer, and other types of cancer, and

this indicates that the bioactive components of this plant might be targeting general cellular processes that many types of cancer have in common, but not causing cancer-associated specific pathways. Most of these have been the antiproliferative effect against lung cancer cells, with research findings indicating that *Cuscuta reflexa* extracts have the ability to substantially lower the viability of A549 human lung adenocarcinoma cells in a concentration-dependent extent, and half-maximal inhibitory concentration rates are within ranges thought to be encouraging in further studies. Equivalent cytotoxic effects have been reported against MCF-7 breast cancer cells, HeLa cervical cancer cells and HepG2 hepatocellular carcinoma cells with varied levels of potency observed between different extracts that is dependent with phytochemical composition [43]. The methanolic and ethanolic extracts which are usually rich in phenolic compounds and flavonoids have often been found to be of greater cytotoxic activity than the aqueous or non-polar solvent extract, indicating that the anticancer principles are concentrated largely in the medium-polarity fraction of the plant phytochemical repertoire. Notably, the cytotoxic effects that are observed are not only cytostatic but in many cases cytocidal, i.e. they do not just arrest the proliferation of cancer cells, but actually kill them, which is essential when it comes to therapeutic applications where it is of paramount importance to eliminate cancer cells [44-46]. The dose-response relationships demonstrated in these studies indicate that *Cuscuta reflexa* extracts usually have bell-shaped or sigmoidal concentration-effect profiles with optimal activity in the intermediate concentrations and weakened action at either very low or very high concentrations in response to the compound effect of multiple bioactive compounds likely with competing or synergistic action mechanisms. All these findings are a strong basis of more mechanistic studies of the anticancer effects of *Cuscuta reflexa* by cellular and molecular mechanisms.

Mechanism based anticancer activity

The mechanism of action of the anticancer effect of *Cuscuta reflexa* has increasingly been explained by in-depth studies that determine the induction of apoptosis as a key mode of action of its cytotoxic activity. Apoptosis or programmed cell death is a physiological process by which the body gets rid of damaged, unwanted or potentially dangerous cells without an inflammatory reaction, and its inhibition is considered one of the major hallmarks of cancer. The fact that *Cuscuta reflexa* extracts can reinstat this dormant cell death program in malignant cells thus makes this property a highly welcome therapeutic attribute [47]. Investigations of A549 lung cancer cells have shed especially close light on the apoptotic pathways activated by Cuscuta reflexa treatment which demonstrate that reactive oxygen species play an essential role in eliciting the cell death cascade. Exposing cancer cells to the *Cuscuta reflexa* extracts induces a rapid and persistent increase of intracellular ROS levels that puts the cell into an oxidative stress situation that surpasses the cellular antioxidant response and activates signaling pathways resulting in cell death through apoptosis [48]. This increase of ROS seems to be an early step in the endogenous process of apoptosis and this occurs before any other of the typical occurrences and it acts as an initial signal that sets into motion the downstream effectors. The role of ROS is experimentally validated by the application of antioxidant pretreatments, including N-acetylcysteine, which are effective in the prevention of *Cuscuta reflexa*-induced apoptosis by blocking the oxidative burst, hence proving the causal relationship between cell death and generation of ROS. This process is consistent with the emerging knowledge that several chemotherapeutic agents, such as older

drugs, such as doxorubicin and cisplatin, also use oxidative stress-mediated apoptosis, by taking advantage of the susceptibility of cancer cells that commonly are subjected to increased basal oxidative stress [49-51].

The visual evidence of apoptosis in the *Cuscuta reflexa*-treated cells is the morphological appearance of apoptotic cells which is a visual confirmation of the biochemical events taking place inside the cell Table 2. The treatment of cancer cells undergoes microscopic observation, which indicates typical apoptotic characteristics that differentiate this type of cell death with necrosis or other cell death processes. These morphological variations consist of cell shrinkage which is a process in which the cell loses volume with the cytoplasmic contents condensing and the cell withdrawing away of its neighbors [52]. The chromatin in the nucleus condenses thus entering a densely packed state that is marginated against the nuclear wall, which is easily observed via nuclear stains like the Dapi or Hoechst dyes that fluoresce when bound to the densely packed DNA. Probably the most unique is the disintegration of the nucleus to several membrane-enclosed apoptotic bodies, which is facilitated by the activation of certain nucleases that cleave the DNA on internucleosomal regions to give the characteristic pattern of the DNA ladder under the gel electrophoresis analysis [53]. Even the cell membrane reorganizes dramatically in the apoptotic process, and phosphatidylserine is typically restricted to the inner layer of the plasma membrane- becoming outside with an eat-me signal given to phagocytic cells. Fluorescently labeled annexin V, a phosphatidylserine binding protein, can be used to detect this membrane change and therefore offers a quantitative method of assessing early apoptotic cells. Blebbing is also observed with the plasma membrane which forms protrusions which eventually segregate to form apoptotic bodies filled with intact organelles and nuclear fragments. These morphological features are constant in various studies using various *Cuscuta reflexa* extracts and different types of cancer cells, which proves the constituents of the plant promote the entire apoptotic program and not mere nonspecific poisoning.

Table 2: Anticancer activity of *Cuscuta reflexa* extracts against different cancer cell lines

Cancer Type	Cell Line	Extract Type	Concentration Range	Observed Effects	Mechanism of Action
Lung cancer	A549 (Adeno-carcinoma)	Methanolic extract	25-200 µg/mL	Dose-dependent reduction in viability, IC50 values in promising range	ROS-mediated apoptosis, mitochondrial depolarization, caspase activation
	A549	Ethanolic extract	50-250 µg/mL	Significant cytotoxicity, apoptotic morphology changes	Nuclear condensation, DNA fragmentation, phosphatidylserine externalization
Breast cancer	MCF-7	Methanolic extract	50-300 µg/mL	Anti-proliferative effects, growth inhibition	Apoptosis induction, cell cycle arrest
	MCF-7	Ethanolic extract	25-200 µg/mL	Cytotoxic activity	ROS generation, mitochondrial dysfunction
Cervical cancer	HeLa	Methanolic extract	50-250 µg/mL	Reduced viability, cell death	Apoptosis induction, membrane changes

	HeLa	Aqueous extract	100-500 µg/mL	Moderate cytotoxicity	Antioxidant-mediated effects
Liver cancer	HepG2	Methanolic extract	50-300 µg/mL	Significant anti-proliferative activity	Apoptosis, Bcl-2 family modulation
	HepG2	Chloroform fraction	25-150 µg/mL	Enhanced cytotoxicity compared to aqueous extracts	Non-polar compound enrichment
Colon cancer	HCT-116	Ethanolic extract	50-250 µg/mL	Growth inhibition, cell death	Apoptosis induction
General observations	Multiple lines	Methanolic/ Ethanolic > Aqueous	Variable	Superior activity in medium-polarity extracts	Phenolic and flavonoid enrichment in polar organic solvents
	Multiple lines	All extracts	Dose-dependent	Bell-shaped or sigmoidal concentration-response curves	

Impact on mitochondrial membrane potential

The key role of mitochondria in regulating apoptotic cell death has made the mitochondrial activity of *Cuscuta reflexa* components a research interest, and studies have continued to indicate that mitochondrial activity inhibition is a major step in the plant anticancer process. Mitochondria are the cell powerhouses, which produce ATP by oxidative phosphorylation, yet play also a role of safeguarding cell survival as they combine various stress signals and identify when a cell survives or dies, it is the process of mitochondrial membrane permeabilization [54]. Normal mitochondria have an electrochemical gradient across the inner membrane with the matrix side being negatively charged compared to the intermembrane space to form a mitochondrial membrane potential, which controls the production of ATP. Such potential is a sensitive indicator of the health and functional state of the mitochondria, and is commonly measured by fluorescent (e.g. JC-1 or tetramethylrhodamine methyl ester) dyes which are accumulated in the mitochondria in proportion to the membrane potential. Upon treating cancer cells with extracts of Cuscuta reflexa, a marked and gradual depolarization of the mitochondrial membrane potential a key commitment point in the apoptotic cascade is seen. Such depolarization is caused by the opening of the mitochondrial permeability transition pore, a large conductance channel, which spans the inner and outer mitochondrial membranes permitting free passage of solutes up to 1500 Daltons, and causing collapse of the electrochemical gradient [55].

The effects of mitochondrial depolarization go much further than the bioenergetic crisis occurring through the absence of ATP production into the cytosol to the release of pro-apoptotic proteins in the mitochondrial intermembrane space in the cytosol. One of these proteins is the cytochrome c which is of particular importance because its release leads to the establishment of the apoptosome a multiprotein complex that includes cytochrome c, Apaf-1, and procaspase-9 that activate the initiator caspase-9 and initiate the proteolytic cascade which results in the demolition of the cells. Some of the other proteins released when mitochondrial permeabilization occurs are Smac/DIABLO, which counteracts inhibitor of apoptosis proteins that would otherwise inhibit

caspase activation and apoptosis-inducing factor, which translocates to the nucleus and facilitates chromatin condensation in an apoptotic-independent fashion [56]. Bcl-2 family of proteins tightly controls the mitochondrial pathway of apoptosis by including pro-apoptotic Bax, Bak, Bid and Bad and anti-apoptotic Bcl-2, Bcl-xL and Mcl-1. Research investigating the influence of *Cuscuta reflexa* to this regulatory system has found a treatment to cause a shift in the balance between pro-apoptotic and anti-apoptotic proteins or both, making mitochondria susceptible to permeabilization. Of special interest is the downregulation of Bcl-2 which is often overexpressed in cancer cells as part of chemoresistance because this process reinstates the capacity of cancer cells to undergo apoptosis in relation to various death stimuli. The depolarization of mitochondrial membrane potential herein observed is therefore not an isolated event but as a result of several upstream signals coming together to focus on the mitochondria and make a final decision to commit to cell death by integrating ROS signaling, p53 activation, and Bcl-2 family modulations into a final decision [57].

Antioxidant and pro-oxidant balance

Cuscuta reflexa and cellular redox status has an interesting paradox which throws light on the complication of pharmacology of plant-based products and the biological actions which vary according to circumstances. On the one hand, comprehensive in vitro studies have shown that *Cuscuta reflexa* extracts have a strong antioxidant property, which can adequately negate free radicals and prevent the destruction of biological molecules by oxidizing agents. The quantification of these antioxidant properties has been done using several standard methodologies such as the DPPH assay that determines the ability to donate hydrogen atoms or electrons to stabilize the DPPH radical, the ABTS assay that measures the radical scavenging ability with respect to the ABTS cation radical, and the FRAP assay that measures ferric reducing antioxidant ability based on the ability to donate electrons [58]. In these tests, *Cuscuta reflexa* extracts are repeatedly shown to have a concentration-dependent antioxidant activity, whose activity is comparable to that of standard antioxidants like ascorbic acid, butylated hydroxytoluene or quercetin. This antioxidant activity is consistent with the high amounts of phenolic compounds and flavonoids in the plant that are established radical scavengers because of their ability to delocalize unpaired electrons throughout their aromatic ring systems as well as to chelate transition metal ions that might otherwise catalyze oxidative reactions. These antioxidant properties are rationally supported by the traditional use of *Cuscuta reflexa* in the conditions linked to oxidative stress, including inflammation, liver diseases, and aging, in which oxidative damage to affected tissues would be predicted [59].

However, ironically, the anticancer properties of *Cuscuta reflexa* take place not by the antioxidant protection but by its exact opposite the formation of pro-oxidant stress which specifically kills cancer cells. This seeming paradox is clarified by the appreciation of the fact that the biological action of polyphenolic compounds is very context-specific, depending on the concentration, cellular context, presence or absence of metal ions, and the redox potential of the target cells. *Cuscuta reflexa* constituents may be indeed effective antioxidants at moderate levels in normal tissues, offering protection against oxidative injury, which explains the traditional roles of the plant in the treatment of conditions related to the presence of oxidative stress. Nevertheless, in the case of increased exposure of the cancer cells to larger

concentrations, or in response to accumulation of the compounds in the microenvironment of the tumor, the compounds may auto-oxidize or can be involved in redox cycling reactions to produce superoxide, hydrogen peroxide and other reactive oxygen species. Such pro-oxidant challenge is especially harmful to cancer cells, which usually work under the conditions of high basal oxidative stress through the combination of high metabolic rate, mitochondrial dysfunction, and activated oncogenic signaling. This prior oxidative stress implied that the cancer cells were already functioning at the border of redox homeostasis, and any further oxidative stress can drive them past the redox homeostasis to cytotoxicity [60]. The increase in the sensitivity of cancer and normal cells to pro-oxidant challenge has created a therapeutic gap that can be used to selectively treat cancer. Moreover, the same phenolic compounds which function as antioxidants under different conditions may undergo Fenton-type reactions in the presence of transition metal ions like copper or iron which are frequently raised in tumors to form very reactive hydroxyl radicals. This is a situation whereby the duo of oxidant and antioxidant, which are context-dependent in normal tissues in physiological conditions, pro-oxidant in cancer cells in conditions of pathologies, is an ideal characteristic of a chemopreventive or chemotherapeutic agent, which may offer protection against carcinogenesis in normal cells and at the same time destroy cancerous cells that have already developed.

Network pharmacology insights

The classical model of drug action based on individual compounds acting on individual molecular targets has become more than satisfactory in the explanation of the therapeutic action of complex botanical extracts such as those of *Cuscuta reflexa*. A newer field, network pharmacology, which integrates systems biology and pharmacology, provides a more advanced model of understanding the interaction of the multiple constituents of *Cuscuta reflexa* with the complex biological networks that comprise the pathogenesis of cancer. This model acknowledges that diseases like cancer are hardly caused by one molecular lesion and that a successful treatment measure can be achieved by regulating a number of nodes in these networks instead of acting on one protein. In the case of *Cuscuta reflexa*, network pharmacology experiments have identified extraordinarily intricate interaction trends of the various phytochemical compounds of the plant and proteins that control the progression of cancer, especially in lung cancer. The computational methods such as molecular docking, network building and pathway enrichment analysis have been used to predict the possible targets of *Cuscuta reflexa* compounds and to map the biological pathways that are most likely to be targeted by the extract [61].

The *Cuscuta reflexa* network pharmacology analysis of the drug in the disease lung cancer presents a more specific image of the multi-targeted mechanism of action of the plant. It involves identifying bioactive compounds in the plant, which is based on the phytochemical profile determined by experimental studies and prediction of possible protein targets of each compound, which is performed using computational tools based on structural similarity to known ligands, inverse docking, or machine learning methods. The compound-target interaction networks that resulted indicate that individual *Cuscuta reflexa* constituents generally touch on several protein targets, and the reverse, which is that individual cancer-related proteins are interacted with by a high number of different constituents, forms a complex web of interactions that together regulate disease-relevant pathways. Among the key

proteins that have been identified to be potential targets are growth factor receptors like EGFR which drives proliferation in most lung cancers, intracellular signaling kinases like PI3K, Akt and mTOR which relay pro-survival signals, transcription factors such as STAT3 and NF-kB that coordinate gene expression programs of inflammation and survival and cell cycle regulators like cyclins and cyclin dependent kinases that manage cell division. The overlapping effect of these various targets by the various components of *Cuscuta reflexa* is combinatoric and can be more effective than the additive effect of individual compound activities, which is likely to be counteracted by redundant and compensatory responses that usually limit the action of single-target drugs [62].

Pathway enrichment analysis of the identified targets indicates that the collective induction of *Cuscuta reflexa* components together with multiple cancer process pathways is observed, such as the PI3K-Akt signaling pathway, the MAPK signaling cascade, the p53 tumor suppressor pathway, and the apoptosis and cell cycle progression pathways. This multi-pathway targeting is especially important in the fact that cancer cells usually respond to parallel survival pathways or acquire compensatory responses to enable them to avoid the actions of agents that act on only one pathway. *Cuscuta reflexa* can potentially produce a lasting and more resistant therapeutic response by acting on several vulnerable nodes in the cancer cell network at the same time. Moreover, network analysis would allow finding out which particular compounds in the complex mixture are the most likely to target the key disease proteins, allowing the prioritization of compounds to be isolated and developed further. The network pharmacology paradigm can also be used to understand why the conventional applications of *Cuscuta reflexa* are not limited to cancer but to inflammatory diseases, liver disease, and other disorders-the same group of targets that is regulated by the constituents in the plant also takes part in a variety of pathological events, and as such their regulation can have therapeutic effects in a variety of disease pathologies. These network-based insights do not just help us better understand the mechanisms of action of *Cuscuta reflexa* but also give a rational basis to mode of production of optimized extracts or combinations of isolated compounds that best maximize therapeutic and minimize toxicity effects. With the further development of network pharmacology approaches, the incorporation of more complex algorithms, larger compound-target interaction databases, and experimental verification of the predicted interactions, our knowledge of the multi-targeted anticancer mechanisms of *Cuscuta reflexa* will continue to grow, and new uses of this fantastic plant may be discovered, as well as improved cancer therapies developed.

THERAPEUTIC APPROACHES AND FUTURE INSIGHTS

Complexity of inflammation and cancer has become one of the most interesting paradigms in the modern oncology, which has essentially transformed the current concept of carcinogenesis and has provided novel platforms of therapeutic intervention. The microenvironment in chronic inflammation, whether caused by an underlying infection, autoimmune disease, or exposure of the environment, is highly favorable to malignant transformation and tumor progression. The relationship between them is so strong that inflammation is currently being treated as an enabling property of cancer- a condition that promotes the acquisition and retention of fundamental hallmarks of malignancy such as persistent proliferation, resistance to apoptosis,

angiogenesis, tissue invasion, and metastasis. The mechanistic connections between inflammation and cancer are multi-faceted and multi-layered: inflammatory cells infiltrating the tissues release the reactive oxygen and nitrogen species that can initiate the direct damage of the DNA directly, leading to mutations in tumor suppressor genes and oncogenes; transcription factors such as NF-kB and STAT3 are activated by pro-inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6, and promote the expression This microenvironment of pro-carcinogenic inflammation is not just a passive background, but an active contributor to the malignant process, and is usurped by growing cancers to assist its progression and invasion. The identification that inflammation is a predictive and a concomitant event in cancer has significant therapeutic implications since agents that can control inflammatory status can be useful in cancer prevention as well as treatment, by interfering with the tumor-favouring microenvironment that enriches malignancy.

In the framework of this concept *Cuscuta reflexa* is a plant of significant interest because it has been seen to mediate inflammatory disorders through several mechanisms that comply with the traditional applications of this plant in inflammatory diseases. The high phenolic, flavonoid and terpenoid content of the plant is a molecular basis of its anti-inflammatory effect which has been confirmed by a series of experimental models. Research into the effect of *Cuscuta reflexa* extracts on the inhibition of inflammatory mediators has shown that it has a significant inhibitory effect on inflammatory mediators such as inhibiting the production of pro-inflammatory cytokines, inhibiting nitric oxide synthesis by downregulating the expression of inducible nitric oxide synthase, and inhibiting the expression of cyclooxygenase-2, the enzyme involved in the production of prostaglandins at inflammatory sites. These effects especially apply to cancer biology since the very same inflammatory pathways involving the activation of NF-kB, STAT3 signaling, COX-2 expression, and cytokine production are the same pathways that tumors use to support a conducive microenvironment. *Cuscuta reflexa* can potentially block the growth factors, survival signals and angiogenic factors supplied to the tumor by inflammatory cells by dampening these inflammatory cascades and inhibit the progression of cancer, even in tumor cells that have no direct cytotoxic effects, without direct action on the tumor. This idea of attacking the tumor microenvironment instead of the tumor per se is a significant paradigm of contemporary oncology as drugs that inhibit angiogenesis or the immune response may be used, and natural products such as those of *Cuscuta reflexa* may have its place in that approach.

Pathway enrichment analysis of the identified targets indicates that the collective induction of *Cuscuta reflexa* components together with multiple cancer process pathways is observed, such as the PI3K-Akt signaling pathway, the MAPK signaling cascade, the p53 tumor suppressor pathway, and the apoptosis and cell cycle progression pathways . This multi-pathway targeting is especially important in the fact that cancer cells usually respond to parallel survival pathways or acquire compensatory responses to enable them to avoid the actions of agents that act on only one pathway. *Cuscuta reflexa* can potentially produce a lasting and more resistant therapeutic response by acting on several vulnerable nodes in the cancer cell network at the same time. Moreover, network analysis would allow finding out which particular compounds in the complex mixture are the most likely to target the key disease proteins, allowing the

prioritization of compounds to be isolated and developed further. The network pharmacology paradigm can also be used to understand why the conventional applications of *Cuscuta reflexa* are not limited to cancer but to inflammatory diseases, liver disease, and other disorders-the same group of targets that is regulated by the constituents in the plant also takes part in a variety of pathological events, and as such their regulation can have therapeutic effects in a variety of disease pathologies. These network-based insights do not just help us better understand the mechanisms of action of *Cuscuta reflexa* but also give a rational basis to mode of production of optimized extracts or combinations of isolated compounds that best maximize therapeutic and minimize toxicity effects. With the further development of network pharmacology approaches, the incorporation of more complex algorithms, larger compound-target interaction databases, and experimental verification of the predicted interactions, our knowledge of the multi-targeted anticancer mechanisms of *Cuscuta reflexa* will continue to grow, and new uses of this fantastic plant may be discovered, as well as improved cancer therapies developed.

CHALLENGES AND CONSIDERATIONS

Although the preclinical results have shown promising signs on the anticancer property of *Cuscuta reflexa*, there are numerous issues which need to be addressed before this botanical resource can be translated into useful clinical therapies. First and most obvious about these difficulties is the very variability in phytochemical composition due to the parasitic nature of the plant, which adds some degree of complexity and variability that is not present in an autonomous plant. Being an obligate parasite, *Cuscuta reflexa* obtains its water, nutrients, and a significant part of its chemical constituents through its host plant, which forms a strong biochemical bond with the specific parasite, and has a significant impact on shaping the phytochemical profile of the latter. Such a relationship results in the host synthesizing secondary metabolites which can be translocated by the haustorial connections and accreted in the tissues of the parasite, and could become part of the phytochemical repertoire of the *Cuscuta reflexa* itself. It implies that the chemical composition of *Cuscuta reflexa* found on various host plants can differ drastically with research recording wide variations in phenolic content, flavonoid profiles and biological activities between the parasite growing on mango, tecoma, acacia or any of the many other plants it can be found on. This host-specific variation does not only involve quantitative differences in the concentration of the compounds but also in qualitative differences in the presence or absence of certain phytochemicals, and certain compounds even occur where *Cuscuta reflexa* feeds on certain host species. This variability is a daunting challenge to those researchers and developers who have to develop reproducible, standardized preparations that can be used in clinical applications because the biological activity of an extract cannot be assured between batches without host plant control and documentation. The seasonal change, geographical location and environment in which the growth occurs provides additional points of complication and as such there is a need to come up with a strong set of quality control parameters that can capture this natural variability and provide uniformity in therapeutic action.

The difficulties of phytochemical variability are also accompanied by the questions of extraction techniques and the standardization of *Cuscuta reflexa* preparations to conduct the research and even use in the therapy. The solvent used in extraction, water, ethanol, methanol, or any other

organic solvent, has significant impacts on the compounds that are extracted out of the plant material and in what relative amounts, and each of the solvent systems yields an extract with a distinct phytochemical fingerprint and a biological activity profile. The solvents that are polar, like water or aqueous ethanol mixtures, extract glycosylated flavonoids, phenolic acids, and other polar ones, whereas less polar solvents, such as chloroform or hexane, extract aglycones, terpenoids, and sterols. The extracts obtained can have qualitatively dissimilar biological properties where there are fractions with strong antioxidant properties and those with good cytotoxic activity on cancer cells due to the different distribution of bioactive compounds with differences in polarities. This change which depends on the solvent makes it difficult to compare studies carried out by various research groups and results in the identification of the particular compounds that cause particular biological effects. Moreover, despite using the same solvent system, in some cases, the change in extraction parameters, such as temperature, time spent, particle size, and solvent-to-material ratio, can have a considerably strong impact on the extraction efficiency and the ultimate extract composition. Lack of universally agreed standards of *Cuscuta reflexa* extraction and characterization implies that every research group is effectively operating with a distinct preparation and restricts generalizability of results and hinders the development of clinical uses. To continue, standardized extraction procedures, approved reference standards, and approved methods of analysis to determine concentrations of marker compounds will be needed in the future to ensure that results can be replicated across studies and a solid basis of therapeutic development can be established.

FUTURE DIRECTIONS

In the future, the study of the anticancer potential of *Cuscuta reflexa* requires further development on numerous complementary axes in order to discover all of its potential as a therapeutic agent. Isolation and characterization of new bioactive compounds of this plant is a priority area of focus because the phytochemical studies carried out so far, though enlightening, must be considered only as tip of the iceberg of the chemical intricacy of the plant. The use of advanced chromatographic methods along with the complex spectroscopic methods such as high-performance liquid chromatography with diode array detection, liquid chromatography-mass spectrometry and nuclear magnetic resonance spectroscopy facilitate the separation and structural elucidation of even trace amounts of compounds, which may result in the identification of new chemical entities with novel mechanisms of action. The identification of two hitherto unreported 2H-pyran-2-one glucoside cuscutarosides A and B is an example of how natural product chemistry can still be useful in drug discovery. In flexible separation Bioassay-guided fractionation, where extracts are separated into fractions of increasing purity which are assayed to investigate biological activity at each stage of the process, offers a logical approach to purification of the isolated compounds mediating any given anticancer activity, whether by cytotoxicity assays, apoptosis induction measurements, or by a mechanism-based screen to detect a particular molecular pathway. These compounds can then be assessed on their respective activities, in comparison to the action of the parent extract to determine whether there might be synergies, and optimized using the tools of medicinal chemistry, i.e. structural modification to achieve increased potency, selectivity, or pharmacokinetic properties, should they have shown attractive therapeutic indices. The

compounds can also be used as chemical probes in the study of biological pathways of interest in the study of cancer and offer a tool in the basic research even though they need not proceed to clinical development.

Lastly, the invention of new drug delivery methods using *Cuscuta reflexa* extracts will overcome a major food-to-drug barrier to use of plant-derived compounds namely poor bioavailability of most plant-derived polyphenolic flavonoids and other solubility-sensitive hydrophilic molecules. Oral administration of these compounds often results in excessive gut and hepatic metabolism to produce low and erratic concentrations to reach systemic circulation and target tissues . It is possible to circumvent these drawbacks using sophisticated drug delivery technologies, which have the potential to access the therapeutic power of *Cuscuta reflexa* bioactives. The compounds can also be encapsulated using nanoparticle-based formulations, such as polymeric nanoparticles, liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, which protect the compounds against premature metabolism, promote absorption of the compounds across the biological barriers and provide sustained or targeted delivery of the compounds to tissue in tumors. The improved ability to target cells to tumor tissue through increased permeability and retention whereby leaky vasculature and deficient lymphatic drainage of tumor tissue favours the accumulation of nanoparticles in tumor tissue is an enhanced mechanism of targeting that may concentrate *Cuscuta reflexa* constituents at the site of action with minimal exposure to normal tissues. More can be done to increase tumor selectivity and cellular uptake with active targeting strategies, which entails the functionalization of nanoparticles with ligands that bind receptors overexpressed on cancer cells. Phytosomes, phospholipid complexes of plant components, are another strategy that is especially relevant to increase the bioavailability of flavonoid glycoside through improving the lipophilicity and membrane permeability of flavonoid glycoside. In topical uses, like skin cancer or tumors easily reached by needle, new methods of formulation like gels, creams and microneedle patches may allow local delivery with minimum systemic exposure. This type of formulation needs interdisciplinary cooperation of pharmacognosist, pharmaceutical scientists, and nanotechnologists, but the reward, which may be a way to turn poorly absorbed natural products into clinically useful medicines, justifies the investment. With all these different avenues of research coming together, the dream of *Cuscuta reflexa* as a safe, effective, and accessible source of anticancer therapy will be brought a bit closer to reality, and one may hope that this parasitic vine will someday start contributing to the treatment of one of the most difficult diseases facing humanity substantially.

CONCLUSION

The thorough overview of the phytochemical and anticancer features of the *Cuscuta reflexa*, which are discussed in this review, makes the given parasitic plant an extraordinarily promising source of lead molecules to be further used in the discovery of anticancer drugs, at the same time proving the critical role of further translation research to bridge the gap between the preclinical opportunities and the clinical usage. The travel via the botanical features, traditional applications, chemical intricacies, mechanistic understanding and therapeutic difficulties, the potential of the natural product that is still unutilized to the full extent, waiting the exact scientific research that could turn traditional information into some evidence-based treatment, is revealed. The phytochemical profile of *Cuscuta reflexa* is a catalog of bioactive compounds that have

established relevance in the study of anticancer antioxidants quercetin and kaempferol flavonols that induce apoptosis through multiple pathways, anti-oxidants chlorogenic acid and dicaffeoylquinic acids with potent antioxidant and pro-oxidant activities depending on context, pro-oxidants and anti-inflammatory agents β-sitosterol and stigmasterol. This chemical diversity is not in vain redundant and it gives the plant the ability to interact with a range of molecular targets at the same time, attacking cancer by parallel perturbation of survival pathways, generation of oxidative stress, targeting of the apoptotic machinery, and regulation of the tumor-promoting inflammatory microenvironment. The network pharmacology data describing intricate relationships between *Cuscuta reflexa* compounds and major proteins involved in cancer-related processes are a contemporary scientific confirmation of the ancient knowledge on which the therapeutic uses of the plant have been based over the centuries proving that the multi-target nature of botanical medicines can be beneficial compared to the single-target paradigm of conventional pharmaceutical development. The evidence that cytotoxic effects occur in a wide variety of cancer cell lines, the explanation of apoptosis induction mechanisms by ROS-mediated mitochondrial depolarization and the apparent antioxidant-pro-oxidant duality of the paradoxical mechanism underlying selective cancer cell killing all point to a strong argument that *Cuscuta reflexa* contains clinically attractive anticancer activity and warrants further research.

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