ABSTRACT

Herbal medicament is one of the most commonly used complementary and alternative therapies by people with chemokinesis. Based on a common belief, herbal medicine with the least possible side effects should be the center of attention in malignancy care; however, in many cases they have not been properly studied with reliable clinical trials in human subjects. Also, the safety of herbal anticancer compounds is discussed. There is currently no strong evidence from studies in people that herbal remedies can treat, prevent or cure cancer. In this review, it was attempted to identify the protagonist role on the use and clinical effects of herbs in malignancy care.

KEYWORDS: Malignancy, Herbs, Prevention, Safety, Chemokinesis.

1. INTRODUCTION

Malignancy is the uncontrolled growth of abnormal cells in the body which invade and destroy nearby tissue and that may metastasize to other parts of the body. Malignant cells are also called as cancerous cells. Cancer is a hyper proliferative disorder that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. Cancers with alarming statistics, cause more than 7 million deaths per year worldwide, more than HIV/AIDS, malaria and tuberculosis combined.[1] Malignancy appears to occur when the growth of cells in the body is out of control and cells divide too quickly. Cancer can develop in almost any organ or tissue, such as the lung, colon, breast, bones, or nerve tissue. Malignancies generally arise because of mutations in the DNA of at least one cell which then behaves abnormally. There are many causes for cancers viz, chemicals like benzene, beryllium, asbestos, vinyl chloride, arsenic etc, drinking excess alcohol, genetic
problems, obesity, radiation, viruses etc. However, the cause of many cancers remains unknown. A growing number of studies indicate that herbal medicine (looking at frequency, type and reasons for use) might have the anti-cancer effect by enhancing the immune system. An important key role for plant medicines in cancer is immunomodulation. Such natural medicines have been reported to serve as biological response modifiers by activating, increasing and restoring the reactivity of immunological effector mechanisms that are involved in resistance to tumor growth and metastasis.

Various therapies have been hypothesized for the treatment of malignancy, many of which use plant-derived products. There are four classes of plant-derived anticancer agents in the market today, the vinca alkaloids (vinblastine, vincristine and vindesine), the epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel) and the camptothecin derivatives (camptotecin and irinotecan). Plants still have enormous potential to provide newer drugs and as such are a reservoir of natural chemicals that may provide chemoprotective potential against cancer. Recently, Taneja and Qazi, have suggested a number of compounds from medicinal plants with potential anti-cancer activities. This review will discuss some of the plant products that have recently been tested and may have potential in anticancer therapies. The possible mechanism of action of such plant products is also discussed.

2. Herbal Medicament and Malignant Chemokinesis

Many studies have focused on the chemoprotective properties of plants such as anticarcinogenic properties of *Abrus precatorius* on Yoshida sarcoma in rats, fibrosarcoma in mice and ascites tumor cells. Similarly, Dhar *et al.* have examined the anticancer properties of *Albizia lebbeck* on sarcoma in mice and *Alstonia scholaris* on benzo[a]pyrene-induced forestomach carcinoma in humans. Other plants that have shown antimalignant properties include *Anacardium occidentale* in hepatoma, *Asparagus racemosus* in human epidermoid carcinoma, *Boswellia serrata* in human epidermal carcinoma of the nasopharynx, *Erthyrina suberosa* in sarcoma, *Euphorbia hirta* in Freund virus leukemia, *Gynandropis pentaphylla* in hepatoma, *Nigella sativa* in Lewis lung carcinoma, *Peaderia foetida* in human epidermoid carcinoma of the nasopharynx, *Picrorrhiza kurroa* in hepatic cancers, and *Withania somnifera* in various tumors. The antimalignant characteristics of a number of plants are still being actively researched and some have shown promising results. Some plants and plant
products that have shown protagonist role in malignant chemokinesis are discussed in detail in the following sections.

2.1: Grape Seed

A research team from the University of Colorado Anschutz Medical Campus, Aurora, had furnished evidence on the efficacy of grape seed extract against colorectal cancer. In this study, the extract from grape seed induced the death of colorectal cancer cells. What's more interesting is the fact that the more advanced the colorectal cancer cells were, the better the grape seed extract suppresses and limits the growth and survival of these cancer cells. The administration of grape seed extract was not only effective against colorectal cancer but also safe to healthy cells of the body.[7]

**Chemical constituents:** Numerous studies have demonstrated that certain nutritive and nonnutritive phytochemicals with potential cancer-preventive or antitumor activity can be isolated from grape seeds. Of these compounds, proanthocyanidins are worthy of mention.

**Grape Seed Extract contains:**

Proanthocyanidins (also known as procyanidins), polymers of catechin (subset of flavonoids) molecules at around 74-78% by weight[8] and sometimes up to 81%[9] of Grape Seed Extract. Specific procyanidin molecules such as Procyanidin B1 (5.3%), B2 (3.1%), and C1 (1.7%) (Different formations of catechin couplets).[9] Free flavonol esters such as epicatechin and catechin (two of the Green Tea Catechins) at less than 6%[8]

Some products may contain other bioactives found in grapes (usually lesser quality controlled supplements), as this study found Resveratrol at 0.53%, rutin at 1.2%, gallic acid at 1.4% and Quercetin as quercetin-3-glucoside at 8%[10]
 Mostly procyanidin polymers by weight, but also composed of the smaller units that make up the polymers.

**Structure**

Grape Seed Extract (GSE) is a mixture of procyanidin polymers, or chains of procyanidins. It appears that some other polymers exist, as (+)-catechin (one of the four Green Tea Catechins) appears to combine in chains to form the main Procyanidin B2.

Grape Seed Extract can contain monomers (one molecule), dimers (two molecules), trimers (three molecules), etc. Most of the bioactivities that are unique to GSE are due to the dimers or larger chains.

**Uses:** Grape seed proanthocyanidins have been found to suppress the potential of pancreatic cancer cells to migrate or spread[11]. Proanthocyanidins have also been reported to inhibit the process of angiogenesis (creation of new blood vessels) induced by colon cancer and to suppress colon tumor growth itself.[12] The proanthocyanidins in grape seed extract act against colon cancer cells, significantly inhibiting cell viability while inducing cell death among cancer cells.[13] Proanthocyanidins can accumulate in high amounts in the colon because they are usually poorly absorbed along the gastrointestinal tract[14]. This is beneficial for the body as this means that grape seed proanthocyanidins can suppress colon cancer more efficiently in the colon.

2.2 Annona squamosa L. (Annonaceae)

![Figure No.2 Seeds of A. squamosa](image)

**Part used:** Seed, Seeds are brownish black, smooth.

**Common Names**\(^{[15]}\): Sanskrit: Bahubijika, Hindi: Sitaphal, English: Custard apple, Marathi: Sitaphal.

**Chemical Constituents**
Numerous acetogenins were isolated from seeds of *A. squamosa*, they are mono- or adjacent bis-THF-rings bearing compounds. Acetogenins belonging to a series of C-35/ C-37, and derived from C-32/ C-34 long chain fatty acids\(^{[16]}\).

A fraction of the MeOH extract contains two adjacent bis-tetrahydrofuran acetogenins named squamocin-O1 (1) and squamocin-O2 (2)\(^{[17]}\). Four new annonaceous acetogenins, dieposabadelin, squamocenin, leprenin and dotistenin were isolated, along with sixteen known acetogenins: corepoxylone, diepomuricanins A and B, dieporeticenine, tripoxyllin, bullatencin, glabrenicin B, reticulatins-1, -2, uvariamicins I, II, III, erythrosolamin, annotemoyin-1 and -2 and solamin\(^{[18]}\). The\(\beta\)-aminosquamocin was isolated from seeds of *A. squamosa*\(^{[19]}\).

It also contains solamin, corossolin, corossolone, murisolin, annonacin, annonacinone\(^{[20]}\). Ketolactone acetogenins Bullatacin, 4-Deoxybullatacin, Bullatacinones, 30-OH -bullatacinones, Asimicin, Trilobacin, Bullatalicin, Bullatalicinones, Annonacin, Isoannonacis were isolated\(^{[21]}\). Annotemoyin-1, Annotemoyin-2, squamocin and cholesteryl glucopyranoside were isolated from the seeds of *A. squamosa*\(^{[22]}\).
Chemical constituents from seeds of *A. squamosa*

Mechanism of Action\(^{[21]}\): The Annonaceous acetogenins have been shown to be potent inhibitors of complex I (NADH: ubiquinone oxidoreductase) of mitochondrial electron transport systems (ETS). It caused tumor cell inhibition by blocking oxidative phosphorylation, limiting the level of ATP and therefore, inducing a type of suffocation (ATP
deprivation) at the cellular level. The acetogenins also selectively inhibit the NADH oxidase activity of plasma membrane vesicles. The second mode of action also lowers intracellular ATP levels by blocking NAD regeneration and, thus, inhibiting glycolytic (substrate level) phosphorylation in the cytosol; these combined modes of action likely lead to apoptosis.

**Uses:** Ripe fruit bruised and mixed with salt is applied to malignant tumors to hasten suppuration. Powder of seeds mixed with gram is a good hair wash. It is given in diarrhea, dysentery and dyspepsia[23]. Seeds, fruits and leaves are effective as insecticide, fish poison, powerful irritant of the conjunctiva and abortifacient[22].

**2.3. Andrographis paniculata (Burm. F.) Nees**

![Figure no.3: Andrographis paniculata](image)

**Parts Used:** Roots and Leaves

**Common Names:** *Andrographis paniculata*, commonly known as bhunimba and kalmegha in Sanskrit, kiryat in Hindi and the king of bitters and chiretta in English, is found in India and Sri Lanka.

**Chemical Constituents:** *A. paniculata* extract contains diterpenes, flavonoids and stigmasterols.[24] The primary medicinal component of Andrographis is the diterpene andrographolide (chemical structure shown below). Andrographolide, described as a "diterpene lactone" due to its ring like structure, has a very bitter taste and has a colorless crystalline appearance. Andrographis leaves contain the highest concentration of andrographolide (~2.25%), while the seeds contain the lowest.[24]
Structure

Mode of Action: Alcoholic extract of *A. paniculata* has been shown to cause a significant increase in the activities of glutathione-S-transferase (GST), DT-diaphorase (DTD), superoxide dismutase (SOD) and catalase, differentially in the lung, liver, kidney and forestomach\(^{[25]}\). It also causes a decrease in the activity of lacate dehydrogenase (LDH) and malondialdehyde (MDA)\(^{[25-28]}\). Andrographis also results in alterations in the level of glutathione (GSH)\(^{[25]}\), and GSH significantly contributes to its function of detoxifying the xenobiotics which may play a causative role in the carcinogenic process.\(^{[29]}\)

Uses: A major chemical constituent of *A. paniculata*, andrographolide has also shown significant anticancer and immuno-stimulatory activities. The *in vivo* results conducted in immuno-competent Swiss albino mice, demonstrated that andrographolide significantly inhibits the cancer cell proliferation without showing any signs of toxicity in mice, even at relatively high doses\(^{[30]}\). Studies conducted on mice have shown that *A. paniculata* is a potent stimulator of the immune system and that it activates both the antigen-specific and non-specific immune responses\(^{[31]}\). Due to its ability to activate both types of immune response, *A. paniculata* is a potent chemoprotective agent and is effective against a variety of infectious and oncogenic agents.\(^{[31]}\) Andrographolide shows cytotoxic activity against a variety of cancer cells.\(^{[32]}\) For example, andrographolide exerts cytotoxic effects against KB human epidermoid cancer cells, P388 lymphocytic leukemia cells, MCF-7 breast cancer cells and HCT-116 colon cancer cells.\(^{[33]}\) Further, andrographolide causes growth inhibition in the colon cancer cell line HT 29, enhances the growth and division of human peripheral blood lymphocytes and exerts pro-differentiative effects on the mouse myeloid leukemia M1 cell line.\(^{[32, 34]}\)
2.4: Azadirachta indica A. Juss (Meliaceae)

Figure No.4 Leaves of A. indica

Part used: Leaves


Chemical Constituents

Number of chemicals isolated from leaves like limoniods and cyclic tri and tetrasulphides. It also contains Azadirachtin, Meliantriol and salanin[^36]. The leaves contain nimbin, nimbine, 6-desacetylnimbine, nimbandiol, nimbolide, quercetin and β- sitosterol[^37].

Active Principle from Leaves of A. indica: Azadirachtin and nimbolide shows potent anticancer activity.

Chemical constituents from leaves of A. indica[^38].
Mechanism of Action\(^{[39]}\)

A substantial number of in vitro studies have demonstrated that the antiproliferative activities of neem extracts and neem limonoids are mediated through inhibition of the cell cycle and induction of apoptosis. Azadirachtin and nimbolide induce cell cycle arrest and apoptosis by targeting a plethora of molecules. Cell cycle arrest is induced by upregulating wild type p53, downregulating proliferating cell nuclear antigen (PCNA) and glutathione S-transferase pi (GST-P), and inhibiting the activation and nuclear translocation of p50-p65 NF-κB heterodimers. Activation of wild type p53 results in the activation and upregulation of its downstream target p21, which in turn results in cell cycle arrest via downregulation of the cell cycle regulators cyclin B and cyclin D1. Inhibition of IκB degradation and nuclear translocation of p50-p65 NF-κB heterodimers cause cell cycle arrest by downregulating various genes involved in cell proliferation. Upregulation of the death receptor Fas and its ligand Fas-L results in the activation of caspases −8 and −3, and apoptosis induction. Azadirachtin and nimbolide also transduce apoptosis by the mitochondrial pathway by increasing the Bax/Bcl-2 ratio, release of cytochrome C from the mitochondria to the cytosol, formation of apoptosome complex, caspase activation and poly (AD ribose) polymerase (PARP) cleavage. In addition, the neem limonoids also enforce nuclear translocation of survivin that enhances its proapoptotic function.

Schematic representation of the potential targets of azadirachtin and nimbolide
Uses\textsuperscript{[40]}: Young leaves are astringent; used in leprosy, skin diseases, rheumatism, leucoderma, piles and reduces inflammation. Young branches are anthelmintic, good for cough, asthma, piles, tumors and urinary discharge. Unripe fruit used in tumors, piles and toothache.

2.5: \textit{Curcuma longa} \textit{L.} (Zingiberaceae)

\textbf{Part used:} Rhizomes

\textbf{Common Names\textsuperscript{[15]}}: Synonym: \textit{Curcuma domestica} Valeton, Sanskrit: Haridra, Hindi: Haldi, English: Turmeric, Marathi: Halkund

\textbf{Active Principle from Rhizomes of \textit{C. longa}:} Curcumin shows potent anticancer activity.

\textbf{Chemical Constituents}

The rhizome contains curcuminoids, volatile oil, sterols, sugars, starch and other polysaccharides. Curcuminoids are the principal coloring agent (6\%) of which curcumin amounts 60\%, with demethoxycurcumin, bis- demethoxycurcumin forming the rest. Volatile oil contains high amount of bisabolene derivatives along with borneol, camphene and $\alpha$-phellandrene\textsuperscript{[37]}. It also contains number of monoterpenes and sesquiterpenes mainly zingiberene, $\alpha$ and $\beta$ tumorone, ar-tumorone\textsuperscript{[43]}. A Novel Sesquiterpene curcumin L is isolated from \textit{C. longa}\textsuperscript{[44]}.
Mechanism of Action\cite{41, 42}

Curcumin suppress multiple signaling pathways and inhibit cell proliferation, invasion, metastasis, and angiogenesis. This polyphenol modulates various targets either through direct interaction or through modulation of gene expression (Figure No. 14). Curcumin physically binds to as many as 33 different proteins, including thioredoxin reductase, COX2, protein kinase C, 5-lipoxygenase, and tubulin. Various molecular targets modulated by this agent include transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis.

Some experiments suggest that curcumin can cause DNA damage either through topoisomerase inhibition or through generation of free radicals however, a direct proof is lacking.

*Figure No. 14: Schematic representation of the potential targets of curcumin*

Uses\cite{35, 37}

The rhizomes are aromatic, carminative, jaundice, liver disorders and urinary diseases. It shows excellent anti-inflammatory, antiulcer, anticancer & antioxidant properties.
2.6: *Emlica officinalis* Gaertn (Euphorbiaceae)

![Figure No. 6 Fruits of *E. officinalis*](image)

**Part used:** Fruit


**Chemical Constituents**

The fruit contain vitamin C (ascorbic acid, upto 2%), gallotannins (5%), carbohydrate (14%), phenolic acids, alkaloids, pectin and minerals. The phenolic acids include Gallic, ellagic and phyllemblic acids and emblicol\(^{[37]}\). The alkaloids present are phyllantidine and phyllantine, zeatin nucleotide and zeatin riboside.

The Benzenoid present are amlaic acid, corilagin3-6-di-O-galloyl-glucoseethyl gallate, 1,6-di-O-galloyl-β-D glucose1-di-O-galloyl-β-D glucose putranjivain A and digallic acid\(^{[45]}\). The triterpene lupeol and Flavanoid kaempherol-3-O-β-D glucoside and quercetin-3-O-β-D glucoside are present.\(^{[46]}\)

**Active Principle from Fruits of *E. officinalis*:** Gallic acid, ascorbic acid shows potent anticancer activity.
Mechanism of Action
Actual mechanism of *E. officinalis* is not known. The activity may be due to interference with cell cycle regulation[47]. Plant derived hydrolysable tannins and gallic acid has been known to kill tumor cells through hydrogen peroxide generation[48].

Uses: The fruits are sour, astringent, bitter, acrid, sweet, cooling, ophthalmic, carminative, digestive, stomachic, laxative, alterant, aphrodisiac, diuretic, antipyretic and tonic. They are useful in vitiated conditions of tridosha, diabetes, cough, asthma, bronchitis, ophthalmopathy, dyspepsia, colic, flatulence, hyperacidity, peptic ulcer, skin diseases, leprosy, inflammations, anemia, jaundice, diarrhoea, dysentery, hemorrhage, cardiac disorders, intermittent fevers and greyness of hair[45]. It exhibits antitumor, antiviral hypotensive, antibacterial & immunomodulatory properties[37].

2.7: *Moringa oleifera* L. (Moringaceae)

![Figure No.7 Leaves of M. Oleifera](image)

Part used: Leaves


Chemical Constituents
Leaves of *M. oleifera* contain amino acid, Vitamin A, 3’-O- Methy l- quecetin, Gossypetin, Quercetagetin and Proanthocynidins. The crude leaf extract contains 4-(α-L-rhamnosyloxy) phenylacetonitrile, Niazinin A and B, Niazimicin A and B, Niaziminin A and B, Niazicin A and B, Niazimin A and B, Niazicinin A, Niazi rinin and Niazipidin[49].
Ethanolic leaf extract of *M. oleifera* contains hexadecanoic acid, ethyl ester (CAS) ethyl palmitate, palmitic acid ethyl ester, 2,6-Dimethyl-1,7-octadiene-3-ol, 4-Hexadecen-6-yn-1, (z)-(CAS), 2-hexanone, 3-cyclohexyliden-4-ethyl – E2- Dodecenylacetate, Hi-oleic safflower oil (CAS), Safflower oil[50]. Fractionated leaf extract contains 4-(α-L-rhamnosyloxy) benzyl isothiocyanate(2), niazimicin(3), niazirin(4), β-sitosterol(5), glycerol-1-(9-octadecanoate)(6), 3-O-(6′'-O-oleyl-β-D-glucopyranosyl)-β-sitosterol(7), and β-sitosterol-3-O-β-D-glucopyranoside(8)[51].

**Active Principle from *M. oleifera* Leaves:** 4-(α-L-rhamnosyloxy) benzyl isothiocyanate (2), niazimicin(3), 3-O-(6′-O-oleyl-β-D-glucopyranosyl)-β-sitosterol(7), and β-sitosterol-3-O-β-D-glucopyranoside(8) shows potent antitumor promoting activity[51].

**Uses**[15]
The leaves are tasty, remove all kinds of pain; anthelmintic; useful in eye diseases, dry tumors, asthma. Leaves pounded and warmed, are applied to tumors as a resolvent. Fruit and
flowers are used in tumors, cures vata and kapha. The ground roots are mixed with salt and applied as a poultice to tumors.


**Parts Used:** root, bark, leaf and fruit.

**Common Names:** This plant is traditionally known as mamaphal in Hindi and sour-sop of America in English, Marathi: Ramphal.

**Chemical Constituents:** The fruit of *A. atemoya* contains bullatacin (chemical structure shown below), an acetogenin. *A. atemoya* contains two annomuricins namely A and B. *A. atemoya* contains several other acetogenins that have also been shown to selectively induce cell death in tumor cells *in vitro*\(^{[52]}\).

![Chemical structure of Bullaticin](image)

**Uses**

The fruit of *A. atemoya* contains bullatacin, an acetogenin known to have antitumor properties. Bullatacin induces chromatin margination and tumor cell condensation, followed by apoptosis\(^{[53]}\). *A. atemoya* contains two annomuricins namely A and B, which have shown cytotoxicity in human solid tumor cell lines A-549 lung carcinoma, MCF-7 breast carcinoma, and HT-29 colon adenocarcinoma cell lines\(^{[54]}\). *A. atemoya* contains several other acetogenins that have also been shown to selectively induce cell death in tumor cells *in vitro*\(^{[52]}\). In particular, two annonaceous acetogenins were found to produce cell death in the human hepatoma cell line HepG2 and hepatoma 2.2.15 cells.\(^{[55]}\)
2.9. *Mappia foetida* Miers. / *Nothapodytes foetida* Miers

**Part Used:** wood

**Common Names:**

**Chemical Constituents:** The active component of *M. foetida* tree wood is camptothecin

![Camptothecine](image)

**Uses:** The active component of *M. foetida* tree wood is camptothecin (chemical structure shown below), a potent chemotherapy drug used to treat leukemia.\(^{[56]}\) Recent studies have indicated that an endophytic fungus which grows on this plant also produces the camptothecine.\(^{[57]}\) Camptothecines have broad spectrum of antitumor activities both *in vitro* and *in vivo*. For example, camptothecines have been shown to be effective inhibitors of nucleic acid synthesis in HeLa cells and L-120 cells.\(^{[58]}\) The anti-neoplastic activity of camptothecine has been attributed to its inhibitory action on the nuclear enzyme type-1 DNA topoisomerase (topo-1).\(^{[59]}\) This alkaloid as well as several semisynthetic or fully synthetic analogues, are in various stages of preclinical and clinical trials.\(^{[59]}\) Irinotecan (7-ethyl-10-[4-(1piperidino)-1-piperidinol] carbonyloxyacamptothecine) is a new potent semi-synthetic derivative of camptothecine, which is active against ascites and solid mouse tumors and induces partial or complete remission of breast carcinoma in the xenograft model system.\(^{[59]}\) A series of Phase II clinical trials have been conducted to assess the anticancer activity of camptothecines and their analogues. The Phase II trials have revealed an extensive range of activities against lymphoma, leukemia, and solid epithelial tumors.\(^{[60]}\) Topotecan, another
synthetic modification of 10-hydroxycamptothecine, has been shown to slow the growth of human colon cancer cells, rhabdomyosarcoma cells, and osteogenic sarcoma xenografts\[59\].

3. CONCLUSION

Any practical solution to controlling the initiation and progression of cancer is of paramount importance. The use of medicinal plant products to manage or arrest the carcinogenic process provides an alternative to the use of conventional allopathic medicine for treatment of the disease. Many herbs have been evaluated in clinical studies and are currently being investigated to understand their tumouricidal properties against various cancers\[61\] and these have been studied. There seem to be emerging approaches that include, not only cytotoxic approaches but also molecular management of cancer physiopathology. The goal in these integrative approaches, which extend beyond eradicating the affected cells, is to control the cancer phenotype. A number of plant-derived products have shown promise in anticancer therapies. Attempts have been made to characterize the effectiveness of single constituents isolated from natural products as chemo-preventive agents. Keeping that perspective in mind, ayurveda which uses a holistic approach in the treatment of disease may provide effective alternative to individual plant isolates in the treatment of cancer. The ayurvedic system of medicine incorporates herbs into its treatment regimens for a number of diseases and disorders. The well-known texts of Charaka Samhita and Sushruta Samhita date back to approximately 1000 B.C. and document the use of plant products in treatment of disease\[61\]. Charaka and Sushruta samhitas, two well-known Ayurvedic classics, describe cancer as inflammatory or non-inflammatory swelling and mention them as either Granthi (minor neoplasm) or Arbuda (major neoplasm). Thus, there is evidence that plant products can have antitumor properties with relatively few side effects. More research on plants and plant-derived chemicals may result in the discovery of potent anticancer agents.

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