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A REVIEW OF ETHNOBOTANY, PHYTOCHEMISTRY, ANTIVIRAL AND CYTOTOXIC / ANTICANCER POTENTIAL OF *MORUS ALBA* LINN.

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ABSTRACT

Morus alba Linn. belongs to family Moraceae commonly known as White mulberry, is one of the old and popular plant esteemed for its wide variety of nutritional and therapeutic values. It has great antiviral and cytotoxic potential. The present review summarizes ethnobotany, phytochemistry, antiviral and cytotoxic / anticancer potential of *Morus alba*. Phytochemical screening of *Morus alba* revealed the presence of flavonoids, glycosides, tannins, polysaccharides and lectins which act as antiviral, cytotoxic and antiapoptotic compounds. To the best of our knowledge, this is the first review focusing on antiviral and cytotoxic potential of *Morus alba* Linn. in detail.

Key words: *Morus alba*, phytochemistry, antiviral, cytotoxicity, anticancer

INTRODUCTION

Since from history plants and herbs are extensively and successfully used for the prevention and treatment of different type of diseases (Wang et al., 2004). In fact, all the nations of world have strong beliefs upon herbs for primary health care because they are economical, easily available and possess more bioavailability with fewer side effects (Mukherjee et al., 2007). Almost 40% of these modernized pharmaceuticals are obtained from plant sources, through natural or artificial processes (Mukhtar et al., 2008: Jassim and Naji, 2003).

Morus alba (MA) commonly known as White mulberry / silkworm mulberry. It is very effective medicinal plant and its different parts are used in different type of diseases. The plant is esteemed for its wide range of medicinal properties like antioxidant, antibacterial, antidiabetic and antiviral. Moreover it is also used in the inhibition or eradication of diseases such as atherogenesis, carcinomas, neurodegenerative disorders as well as skin ailments (Butt et al., 2009). MA leaves are also effective as antibacterial, antihypertensive and antiviral (Zhou and Huang, 2007). Active constituents of mulberry leaf are polysaccharides which has potential to decrease blood glucose level and blood pressure. Moreover it also controls immune system

(Alamo et al., 2004: Kodama et al., 2004). Synonyms of the plant along with its vernacular names are mentioned in **Table 1** (Lim 2012).

Table 1: Synonyms and vernacular names of *Morus alba* Linn

Synonyms: *M. tatarica* L., *M. pumila* Balb., *M. multicaulis* Perr. and *M. rubra Lour*. Arabic: *Al tooth* Chinese: *Bai sang, hong sang, sang bai, sang Zhi* English: White mulberry,ChineseWhite-Mulberry. Greek: Aspri moria India: Toot, chimmi, shehtoot, tutri Italian: Gelso bianco	Sansakrit: Toota, Brahmataru, Tooda Tamil: Kambli Chedi Unani: Shahtuut, Tuut. Japanees: Kuwa, Guwa, Ma guwa Pakistan: Tut, tut kishmishmi, tutri

Figure 1: Tree & Leaves of Morus alba

1.1. **Habitat:**

Morus alba commonly known as White mulberry belongs to family Moraceae. Common names are *Tuta*, *Toot* and Shehtoot. The plant is of short life span, rapidly growing, small to medium size tree, growing about 10 to 20 meter tall. Its species are innate to Northern China, and is extensively growing everywhere. The bark is gray and thick, with many irregular longitudinal cracks. Fruits are grown in deep purple to red subovate color during May to August. It has about 10 to 16 species which are generally known as Mulberries (Oka and Ohyama, 2012). The taxonomical classification of the plant is exemplified in **Table 2.**

1.2. Traditional uses:

Among the mulberries, white mulberry is very common and extensively farmed as ideal fodder for the nourishment of silkworms which is involved in industrial silk production (Taylor et al., 2005). On the other hand, leaves are also used as foodstuff for livestock (cow and sheep) in restricted areas. The fruits are edible and tasty. Leaf juice of white mulberry can be preventive for different throat infections. Bark is very helpful in different type of diseases like cough,

decongestion, swelling and anuria. Moreover this is also intended in fever, red eyes, sore eyes and pain. Root bark has cathartic properties. MA has been used as important medicinal plant in Chinese medicines since 659 AD. Therapeutic uses of different parts of MA are mentioned in the Pharmacopoeia of the People's Republic of China. In addition it is also reported in the British Herbal Pharmacopoeia.

Table 2: Taxonomical classification of *Morus alba* Linn.

Kingdom: Plantae
Subkingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Hamamelididae
Order: Urticales
Family: Moraceae
Genus: Morus
Species: *Morus alba*

Source: The Plants Database. (http://plants.usda.gov, 23 March 2012)

Traditionally, fruit juice of MA is widely used in jaundice and liver problems in different regions of Pakistan (Abbasi et al., 2009). Fruit of *Morus alba* is very beneficial in kidney diseases, hair problems, weakness, fatigue, constipation, blood disorders, anemia and premature graying of hair. In addition, fruit juice has been reported for treatment of fever and intestinal worms (Kumar and Chohan, 2008: Yamatake et al., 1976).Different parts of MA has been extensively used in folk medicine of different countries (Pakistan, China, India) for different diseases like diabetes, throat infections, edema, wound healing (Anonymous, 1952). In folk medicine, people use infusion of MA bark as laxative, cathartic and purgative. Due to the presence of phenolic constituents plant is very effective in hypoglycemia as well as an antioxidant (Yadav et al., 2008). The tree and leaves of MA are shown in **Figure 1.**

1.3. Chemical constituents:

Morus alba is a rich source of natural occurring chemical constituents. . Phytochemical tests of different parts of *Morus alba* revealed the presence of alkaloids, flavonoids, saponins, polysaccharides and tannins, which are responsible for diverse pharmacological activities of the plant. *Morus alba* leaves are enriched with numerous nutritional and medicinal constituents such as carbohydrates, fibers, vitamins, minerals, protein, tannins and fats. About 14% to 18% of proteins contents are reported in *Morus alba* leaves found in Pakistan (Andreoni, 2005). Nevertheless, different type of significant flavanes and their glycoside were also extracted from

the leaves (Kayo, 2001). A list of major constituents isolated from different parts of the plant and its major activity is depicted in **Table 3.**

Table 3: Chemical constituents isolated from different parts of *Morus alba* Linn.

Part Used	Active constituent	Activity	Reference
Roots bark	Kuwanon G, Albanol A, Moracin and mullberroside A Polyhydroxylated alkaloids: (2R,3R,4R)-2- hydroxymethyl-3,4-dihydroxy-pyrrolidine-N-propionamid, 1-deoxynojirimycin (DNJ), moralbanone, kuwanon S, mulberroside C, cyclomorusin, eudraflavone B hydroperoxide, oxydihydromorusin, leachianone G and alpha-acetyl-amyrin, Mulberrofuran G and albanol B Oran 20k	Anti-cough, decongestion, swelling and anuria. Fever, red eyes, sore eyes and pain. Root bark has cathartic properties. Infusion of MA bark as laxative, cathartic and purgative.	Kayo, 2001 Asano et al., 2001 Oku et al., 2006 Du et al., 2003 Kim et al., 2013
Leaves	scopolin , isoquercitrin, skimming, astragalin, roseoside and benzyl glucopyranoside phenolic acids such as gallic, protocatechuic, p-hydroxybenzoic, vanillic, chlorogenic, syringic, *p*-coumaric, ferulic and *m*-coumaric acids , DNJ (Deoxynojirimycin) Polysaccharides Ascorbic acid, carotene, vitamin B1, folic acid, folinic acid, and vitamin D. Volatile constituents: n-butanol, betagamma-hexenol, methyl-ethyl acetaldehyde, nbutylaldehyde, isobutylaldehyde, valeraldehyde, hexaldehyde, alpha-beta-hexenal, methyl-ethyl ketone, methyl-hexyl ketone, butylamine, and acetic, propionic and isobutyric acids. Calcium malate, succinic, and tartaric acids, xanthophyll and tannins Minerals: Calcium, phosphorus, magnesium, Magnese, zinc rutin, isoquercitrin, astragalin and quercetin-3-(6- malonyl) glucoside Katsube *et al.*, Polyphenolics: Caffeoylquinnic acid, Caffeic acid, 5-caffeoylquinnic acid, 4-Caffeoylquinnic acid, Quercetin-3-O-rhamnoside -7-O-glucoside , Quercetin-3,7-D-O-β-D-glucopyranoside, Kaempferol-7-O-glucoside , Rutin, Quercetin-3-O-glucoside, Quercetin-3-O-(6-malonyl)- β -D-	For Hypoglycemia as well as an antioxidant	Memon et al., 2010 Nuengchamnong et al., 2007 Anonymous, 1952 Kayo, 2001 Katsube et al., 2010 Oku et al., 2006 Koshihara et al., 1984 Thabti et al., 2012 Jia et al., 2013 Yang et al., 2010 Kostic et al., 2014, Kim et al., 2013

	glucopyranoside, Quercetin-3-O-glucoside-7-O-rhamnoside, Kaempferol-3-Oglucopyranosyl-(1,6)- β –Dglucopyranoside, Kaempferol-3-O-(6-malonyl)glucoside Pyrrole Alkaloids: Morrole A, Cyclomulberrin and cyclocommunol, Morusinol (prenylated flavonoid), Morusin and Cyclomorusin,Deguelin		
Fruit	Phenolics, flavonoids, ascorbic acid, minerals Fatty acids: linoleic acid, palmitic acid and oleic acid Polyydroxyalkaloids: 4-O-α-Dgalactopyranosyl- calystegine B2 and 3β,6β-dihydroxynortropane Anthocyanins: cyanidin 3-O-(6''-O-α-rhamnopyranosyl-β-D-glucopyranoside), cyanidin 3-O- (6''-O-arhamnopyranosyl- β-D-galactopyranoside), cyanidin 3-O-β-D glucopyranoside, cyanidin 3-O-β-Dgalactopyranoside and cyanidin 7-O-β-D-glucopyranoside	For Hypoglycemia as well as an antioxidant. Jaundice and liver problems.Kidney diseases, hair problems, weakness, fatigue, constipation, blood disorders, anemia and premature graying of hair. In addition, fruit juice has been reported for treatment of fever and intestinal worms.	Rcisli and Orhan, 2007 Zhang et al.,, 2008 Tian et al., 2007

1.4. Antiviral activities:

Viral infections including infectious and non-infectious are global health problem and for the eradication of such infections no considerable antiviral agents are available (Esimone etal., 2007). In addition, problem of emerging resistance to such viral diseases is also rising day by day. So there is a great need of identifying new type of antiviral drugs from herbal origin to overcome these problems (Martin and Ernst, 2003). Various plants reported to have antiviral properties against different type of viruses such as RNA and DNA viruses (Naithani et al., 2008). *Morus alba* is one of the worthy plant due to its antiviral properties.

Eight different ingredients were separated from the *Morus alba* (root bark) including one flavonoid known as moralbanone. The antiviral activities of these ingredients were evaluated against herpes simplex type 1 virus and their structures were illuminated. It was concluded by Leachianone G, one of these eight compounds possess very strong antiviral property with IC_{50} (inhibitory concentration 50%) of 1.6 μg/ml. Moreover another ingredient among these eight compounds was found to have little activity against virus that is its inhibitory concentration was determined as 75.4 μg/ml (Du et al., 2003).

In a study, a silkworm (*Bombyx mori*) extract known to contain naturally occurring iminosugars, including 1-DNJ derived from the mulberry tree, were evaluated in surrogate HCV (Hepatitis C virus) and HBV (Hepatitis B virus) in vitro assays. Antiviral activity of the silkworm extract and one of its purified constituents, 1-DNJ was demonstrated against bovine viral diarrhea virus and GB virus-B, both members of the Flaviviridae family. The silkworm extract exhibited a 1,300 fold greater antiviral effect against BVDV (Bovine viral diarrhea virus) in comparison to purified 1-DNJ. Glycoprotein processing of BVDV envelope proteins was disrupted upon treatment with the naturally derived components. The glycosylation of the Woodchuck hepatitis virus (WHV) envelope proteins were affected largely by treatment with the silkworm extract than with purified 1-DNJ as well. Studies showed five constituent iminosugars found in the silkworm extract were responsible for antiviral effects observed for the inhibition of intact maturation of hepatitis viral particles and may complement conventional therapies (Jacob et al., 2007). Another study reported the presence of polysaccharide in MA leaves (Zhen et al., 2003) which possess antiviral activity (Galhardi et al., 2012).

Root bark is also enriched in Mulberrofuran G and Isomulberrofuran G, two Diels-Alder-type isomers showed moderate anti-HBV activity through many spectroscopic techniques. Total analysis along with HepG 2.2.15 cell line *in-vitro* testing, ensured its capability to inhibit hepatitis B virus DNA replication with inhibitory concentration over 50% populations of 3.99 µM (Geng et al., 2012).

Additionally, mulberry juice investigation proved its antiviral activity particularly against murine norovirus-1 (MNV-1) and feline calicivirus-F9 (FCV-F9). The two viruses are considered to be human experimental surrogates of human norovirus, used to test the inhibitory effect of mulberry juice against its cytopathic effects. MA juice in concentration of 0.005% and 0.25% (with respect to 100%) was identified to be effective in reducing the infectivity and replication of two examined viruses respectively. Cyanidin-3-glucoside and cyanidin-3-rutinoside, polyphenolic components of *Morus alba* juice, were concluded as preventive of foodborne viral infections in this study (Lee et al., 2014).

Phenols and bioflavanoids are the major classes with antiviral activity against various diverse virus families such as retroviridae, hepadnaviridae, hespervirides, HIV virus, influenza virus, herpes simplex virus, dengue virus, polio virus (Pooja and Anjoo, 2012).

Phytochemical tests of *Morus alba* leaves revealed the presence of flavonoids specially flavane and isoquercetin (Kayo, 2001), saponins and tannins, and earlier reports of chemical constituents and their pharmacology suggest that the plants containing flavonoids, saponins and tannins possess antiviral activity against many viruses. Flavonoids present in MA leaves revealed in vitro antiviral activity against HIV(Luo et al., 1994)[1], rabies virus and herpes simplex virus (Farkas et al., 1986). Moreover evidence has accumulated that iminosugar derivatives exert antiviral effects against several viral pathogens including HIV (RNA virus), HBV (DNA virus), Dengue (RNA virus) and Japanese encephalitis viruses (RNA virus) (Durantel et al., 2001). D-Fagomine (1,2-dideoxynojirimycin) is a six-membered ring iminocyclitol present in *Morus alba* leaves (Asano et al., 2001). Nevertheless DNJ was also reported in the mulberry leave extract (Nuengchamnong et al., 2007) found to be effective in the treatment of AIDS (Sergio, 1989: Oku et al., 2006). Derivatives of 1-deoxynojirimycin (1-DNJ) demonstrate antiviral effects in vitro (Block et al., 1994: Zitzmann et al., 1999).

Different type of viruses such as herpes simplex virus type I, II and modern communicable viral infections are rendering hard time for human beings. So in such circumstances MA could be a future lead for development of antiviral drugs with broad spectrum of antiviral activity, increased safety margin, good quality, less resistance and fewer side effects.

1.5. Cytotoxic / Anticancer potential

In a study a prenylated flavanone named 7, 2', 4', 6'-tetrahydoroxy-6- geranylflavanone, was isolated from ethyl acetate extracts of *Morus alba* root. This novel prenylated flavanone exhibited cytotoxic activity against rat hepatoma (dRLh84 cell line) with an inhibitory concentration over 50% (represented as IC_{50}) of 52.8 mg/ml (Hisayoshi et al., 2004).
Additionally another flavanone glycoside, 5,2′-dihydroxyflavanone-7,4′-di-*O*-*β*-*D*-glucoside (steppogenin-7,4′-di-*O*-*β*-*D*-glucosiade), was isolated from the root bark of MA which resulted in cytotoxic activity (IC_{50} = 3.68 μmol/lit) against human ovarian cancer using HO-8910 cell line (Zhang et al., 2009).

Chon et al., 2009 determined antiproliferative activity of methanolic extracts of *Morus alba* leaves against human pulmonary carcinoma, human breast adenocarcinoma and human colon carcinoma using Calu-6, MCF-7 and HCT-116 cell lines respectively (Chon et al., 2009).

In another study, Kikuchi et al., 2010 demonstrated that Albanol A from the root bark of Morrus alba had anti proliferative capability against HL-60 (human leukemic) cell line, which was analogous to Cisplatin with an IC_{50} of 1.7 μM and 1.9 μM respectively. Although the other tested compound Mulberrofurane Q: (IC_{50} = 37.6uM) showed strong anticancer potential. The suggestive mechanism for apoptosis induction regarding Albinol A was topoisomerase II inhibiton (IC_{50} = 22.8uM) which was comparable to Etoposide, inspite of the fact that Albinol A had much lesser potency on Topoisomerase I (88.4 μM). In addition Kikuchi and co workers also suggested that Albinol A had capability of inducing apoptosis via cell death receptor pathway.

Anticancer effect of mulberry leaf extracts was also evaluated in a study using human hepatoma HepG2 cell line. Different type of leaf extracts of *Morus alba* were prepared. Different parameters including cytotoxicity, apoptosis, expression of topoisomerase IIα, and cell cycle progression were investigated. For HepG2 cell inhibition, IC_{50} values were found to be 33.1, 79.4, 35.6, and 204.2 μg/mL for 100% methanol, 50% methanol, butanol and water extracts respectively. It was concluded that phenolic rich organic extracts of MA leaves had anti-proliferative potential against HepG2 hepatoma cells via cell cycle arrest in the G2/M phase, caspases release and topoisomerase IIα inhibition (Naowaratwattana et al., 2010).

Additionally a lectin (known as MLL) isolated from *Morus alba* leaves showed anti-proliferative activity (IC_{50} = 8.5 μg/ml) against MCF-7 (breast cancer cell line), underperforming relative to Cisplatin (2 μg /ml). Same MLL lectin also resulted in cytotoxicity and cell cycle arrest in HCT-15 (colorectal cancer cells) with an IC_{50} value of 16 μg/ml, underperforming relative to Cisplatin (1 μg/ml). The reported apoptosis induction mechanisms were associated with Caspase-3 release (Deepa and Priya, 2012).

In another study conducted in Egypt, three compounds (marked as 1, 2, & 3) were isolated from root of *Morus alba* . Their structures were elucidated and they showed significant cytotoxic potential against Cervix (MCF7 cell line), Breast (HELA cell line) and Liver (HEPG2 cell line) cancers with IC_{50} values of 0.71 0.92 0.89, 0.56 1.41 0.97 and 0.52 0.45 0.68 respectively (Meselhy et al., 2012).

Three prenylated flavonoids, kuwanon E, cudraflavone B, and -O-methylkuwanon E isolated from *Morus alba* were tested for cytotoxic activity against THP-1 cells. Cudraflavone B, one of the three flavonoids exhibited potent cytotoxic and antitumor activity on proliferation of THP-1 cells. On the other hand, rests of flavonoids were moderately capable for antiproliferative activity against THP-1 cells (Kollar et al., 2013).

Organic and aqueous extracts of MA leaves especially the 100% methanolic extract, were reported to inhibit cell proliferation, modulate the biochemical markers of differentiation and malignancy, and capable of inducing cell morphological changes toward more mature forms of hepatocytes of HepG2 cells. These findings altogether show that the organic and aqueous extracts of mulberry leaves are of value for further exploration as a potential anticancer agent (Fathy et al., 2013).

Later, in 2015, Qin and co- workers isolated few more potential components from root bark of *Morus alba* . Out of these identified molecules, six are Diels-Alder adducts (marked as compound 1-6) and remaining nine are prenylated flavonoids (represented as 7-15). Soroceal B (compound 1) and Sanggenol Q (compound 7) were found to be unique in their structures, identified through NMR techniques. Majority of these fifteen compounds divulged its anti-tumor activity, explored after testing it against five different human tumor cell lines.

Previously, anti-proliferative effect of *Morus* methanolic extract had already been identified through human colon cancer and breast cancer cell lines. The inhibitory potentials of 13.8 µg/mL and 9.2 µg/mL were found to be effective against two cancers, respectively. However, HPLC based analysis of methanolic extract revealed its composition and categorized as major (epicatechin, myricetin, quercetin hydrate, luteolin, and kaempferol) and minor (ascorbic acid, gallic acid, pelargonidine, and p-coumaric acid) components. The concept of anti-cancer activity of *Morus alba* was taken from this study to pursue recent anti-tumor based activity (Deepa and Priya, 2012: Deepa et al., 2013).

Table 4: Possible antiviral, cytotoxic and anticancer constituents of *Morus alba* with their mechanism

Antiviral constituents with their mechanism	**Cytotoxic constituents with their mechanism**	**Anticancer constituents with their mechanism**
Flavonoids: Quercetin Targets entry of virus into the host cell as well as inhibition of translational process during virus replication (Kaul et al., 1985) **Iminosugars:**	**Flavonoids: Kuwanon E, cudraflavone B** Production of toxic oxygen species which results in cell death (Matsuo et al., 2005)	**Glycosides:** Cell cycle arrest(Zhang et al., 2009) **Lectin:**

deoxynojirimycin (DNJ) Blocks morphogenesis in viral replication cycle (Durantel et al., 2001) **Tannins:** Inhibits entry of viral particle into the host cell (Jassim and Naji, 2003) **Polysaccharides:** Interfere with attachment of virus with the host cell (Talyshinsky et al., 2002)	**Saponins:** Interference with cell growth (Kaul et al., 1985) **Phenolic compounds:** Interference with oxidases, group of enzymes and hence causes toxicity to cells (Memon et al., 2010).	caspases release (Deepa and Priya, 2012) **Polyphenolics : Albanol A/ Mulberrofuran G** topoisomerase II inhibition, caspases release, cell cycle arrest, induction of apoptosis, inhibition of angiogenesis, apoptosis via cell death receptor pathway (Naowaratwattana et al., 2010)

MA leaves contains flavonoids and some flavonoids are cytotoxic at higher concentrations (Du et al., 2003 : Matsuo et al., 2005). Yang et al.,. (2010) reported that some flavonoids constituents present in ethanolic MA leaves extract showed cytotoxic activity against A549, Be17402, BGC823, HCT-8 and A2780 cell lines in vitro by MTT method. In another study phenolic acids such as gallic, protocatechuic, p-hydroxybenzoic, vanillic, chlorogenic, syringic, *p*-coumaric, ferulic and *m*-coumaric acids were reported in MA leaves (Memon et al., 2010) [51,52]. Phenolic agents were reported to be cytotoxic by affecting DNA synthesis, RNA reductase and microsomal mixed-function oxidase (Wick, 1980a : Wick, 1980b: Fitzgerald and Wick, 1983: Fitzgerald and Wick, 1985: Passi et al.,, 1987: Riley, 1984). In cell cultures some phenols readily oxidized and cause cytotoxic effect by generation of toxic oxygen species (Parson, 1985 : Picardo et al., 1987). It might be some flavonoid constituents or phenolic acids which could be responsible for cytotoxic potential of MA.

Possible phyto-antiviral, cytotoxic and anticancer constituents of *Morus alba* L. with their mechanism are summarized in **Table 4.**

CONCLUSION

A review of ethnobotany, phytochemistry, antiviral and cytotoxic / anticancer potential of morus alba linn.was described.The review intimate the therapeutic uses of the medicinal plant and its constituents in blood and liver disorders including diabetes,hypertension and CNS.The use of Plant as hepato-protective and in cardiac illnesses is scientifically sound and valid. Still there are so many possibilities to explore the anonymous potentials of the plant based on its uses.

The reviewers focused on the antiviral and cytotoxic/anticancer activity of Plant and emphasized to pay attention for the isolation of newer molecules which will be helpful for the advancement in therapeutics use of plant and in improvement of quality of life.

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