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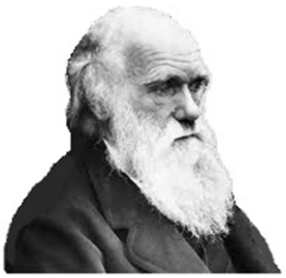

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Therapeutic effects of *Cucumis metuliferus* fruits on avian viruses

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ABSTRACT

Poverty is the major restraint of people to modern medicine in the developing world. This brought about therapeutic usage of medicinal plants which can be traced back to history as different cultures utilize plants and plant products from ancient time for preventing and treating of diseases. These People in the developing countries or rural areas solely depend on traditional medicine for their primary health care, in which they majorly use plants or their active principles. Upsurge resistance of avian viruses to commercial drugs is both developed and developing countries problem which imposed a search for new avian antiviral substances from other sources like medicinal plants. This led to the discovery of *Cucumis metuliferus* E. Mey. ex Naudin fruit which has been verified by local farmers and scientific researchers to cure various diseases and conditions including avian viruses like Newcastle Disease Virus (NDV), Infectious Bursal Disease Virus (IBDV), avian influenza and Hepatitis B Virus. This review is aimed at revealing the avian virus diseases that are treated with the *Cucumis metuliferus* E. Mey. ex Naudin, fruit and phytochemical constituents responsible for this antiviral activities.

Keywords: Therapeutic, Poverty, Traditional medicine, resistance, *Cucumis metuliferus*

1. INTRODUCTION

The use of plants for various purposes have started since ancient times (Lawrence and Bennett, 1995) and the study of medicinal herbs are increasing by pharmacological researchers (Sinclair, 1998). Not until recently, more attention of people were drawn to these practices all over the globe. About 700 medicinal plants have been used for herbs in India as early as 1900

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BC (Aggarwal *et al*., 2007). Herbal medicine was also essential from early days in Africa, Asia and Europe.

According to the World Health Organization (WHO), above 80% of the world's population count on herbal medicine for their main healthcare, majority use plants or their active ingredients (Gupta *et al.*, 2005). All over the world, people intensely believe in the use of plants for many things, like food, forage for their animals, herbal medicine, shade and fire, etc. For example, the tribal people of Panama still rely solely on therapeutic powers of plants, due to the difficulty in getting modern healthcare for their day-to-day problems, even though the western medicine has been present in the region since the seventies (Gupta *et al.*, 2005); Zulu medicinal plants are traded and used all over South Africa (Lin *et al*., 1999).

Many plants are used in Africa for the treatment of different diseases of man and animals, such as coccidiosis (Usman *et al*., 2014), diarrhoea (Sodipo *et al.*, 2005), tuberculosis (Ofukwu *et al.*, 2008), skin diseases (Harsha *et al*., 2003), hyperlipidemia (La Cour *et al*., 1995), salmonellosis (Geidam *et al*., 2007), fever (Devi *et al*., 2003), dysentery (Hernández *et al*., 2003), and others which are typical diseases of a tropical country (Silva and Fernandes Jr., 2010). Reports of various plants used in the treatment of diseases have been documented in Nigeria (Alawa *et al*., 2008), Togo (Beloin *et al*., 2005), South Africa (Rabe and van Staden, 1997; Lin *et al*., 1999), Uganda (Hamill *et al*., 2003), Kenya (Fabry *et al*., 1998; Matu and van Staden, 2003), Ethiopia (Gedif and Hahn, 2003), India (Harsha *et al*., 2003; Nandagopalan *et al*., 2011), Belize (Camporese *et al*., 2003), Turkey (Yeşilada *et al*., 1995), Columbia (Ritch-Krc *et al*., 1996), Panama (Gupta *et al*., 2005), Italy (Guarrera, *et al*., 2005), Mexico (Hernández *et al*., 2003), Australia (Semple *et al*., 1998).

Increased attention on ethnoveterinary medicine (EVM) is justified because it is accessible, easy to prepare and administer at little or no cost at all (Jabbar *et al.*, 2005). These practices may be the only option in areas where conventional services are economically unavailable or cannot be effectively reached (Mathias and McCorkle, 2004). Many EVM practices do work and make sound veterinary sense (Schillhorn van Veen, 1996). Herbal medicines are known to be broad spectrum and therefore may be a future answer to pathogen resistance to conventional drugs (Mwale *et al.*, 2005). These have necessitated a search for new antiviral substances from other sources including plants (Erdogrul, 2002). The use of plant resources mainly for herbal medicine, food, forage, etc. in Nigeria represents a long history of human interaction with the environment and their *in vitro* and *in vivo* properties to microbial pathogens have been widely reported (Hashish and Gomaa, 2003; Iwalokun *et al.*, 2004). These herbs have many potential clinical and therapeutic applications in the modern medical setting, as numerous studies have revealed that they contain bioactive components, which have resulted in a better understanding of their physiological, therapeutic and clinical actions (Merken *et al.*, 2001; Zheng and Wang, 2001; Mikołaj Kostryco, *et al.*, 2017).

Cucumis metuliferus plant belongs to the family of Cucurbitaceae, and is a monoecuous, climbing annual herb, with staminate flowers typically appearing several days before pistillate flowers. The fruit is bright yellow-orange in colour when mature, consisting of greenish juicy bland tasting tissues (Sulaiman *et al.* 2011; Benzioni *et al.* 1993). The widely use of the plant as food and for medicinal purposes have been documented (Jimam *et al.* 2011; Roodt 1998). The fruit of the non-bitter variety of *C. metuliferus* has been found to be less toxic and cultivated on large scale for consumption by the local populace (Benzioni *et al.* 1993). The fruit of the plant was also used during the bird flu (avian influenza) outbreak by some local farmers in Plateau State, Nigeria, with some level of success and the antiviral properties of the ethanolic

fruit extract had been reported on Newcastle Disease Virus (NDV-K and NDV-I) (Wannang *et al.* 2010).

In this review, a survey on current experiment on Phytochemial constituents and therapeutic effects of *Cucumis metuliferus* on avian viruses will be discussed.

1. 1. The Plant Description and Distribution

Cucumis metuliferus belongs to the family Cucurbitaceae. It is commonly referred to as African horned cucumber, jelly melon. *Cucumis metuliferus* is an annual climbing or rarely trailing herb; vegetative parts are rough with spreading hairs. Stems are up to 3 m long, radiating from a woody rootstock. The leaves are broadly ovate cordate in outline, up to 90 × 100 mm, unlobed or usually palmate 3–5-lobed, margins minutely toothed; leaf stalks (petioles) up to 100 mm long. Both male and female flowers appear on the same plant (monoecious). Male flowers are solitary or up to 4 in sessile or short-stalked groups, greenish to light yellow, the corolla is 5–10 mm long. Female flowers are solitary on 20–60 mm long stalks; the ovary is up to 20 mm long, pale green with numerous minute, dark green, fleshy spines, the corolla is yellow, 8–15 mm long.

The fruit is trigonous (triangular in shape), 60–150 mm long, 30–60 mm across when ripe, the scattered spines are rather stout, fleshy, 10 × 2–5 mm, broad-based, deep green-grey, ripening yellow to orange-red with obscure longitudinal stripes of small pale markings and rather softly fleshy. Seeds are ellipsoid, flattened, 6–9 mm long, numerous, embedded in a light green or emerald-green, jelly-like flesh (Burkill, 1985). *Cucumis metuliferus* grows naturally in tropical Africa south of the Sahara down to Senegal, Nigeria, Namibia, Botswana, South Africa and Swaziland. In Nigeria, it is found in Jos, Plateau State. In South Africa it is found in Limpopo, Mpumalanga and KwaZulu-Natal.

It has also been recorded in Yemen and is occasionally cultivated in South Africa and elsewhere. This specie usually grows in shallow or deep, well-drained sand, mostly in alluvial soil on river banks, in river beds or flood plains; it is also recorded from clay or loam soil and rocky slopes. It climbs on trees, shrubs or grass in various vegetation types such as forest edges (often riverine), ellipsoid-cylindrical, obscurely semi evergreen forest, deciduous woodland (often with *Acacia*), savanna or grassland. The jelly melon also grows in disturbed areas and abandoned land (Burkill, 1985).

1. 2. Various Species of *Cucumis*

Cucumis is a genus of vines in the gourd family, Cucurbitaceae. It includes many important food plants, such as cucumber, muskmelon, and kiwano melon. *Cucumis sativus*, or the cucumber, and *Cucumis melo*, or muskmelon, are both widely cultivated. The muskmelon, or true melon, has many varieties, including cantaloupe and honeydew (Burkill, 1985). *C. sativus*, the cucumber, originated in India, and is now cultivated throughout the world. Many different varieties have also been developed. The cylindrical fruit, mix in cuisine as a vegetable, is eaten when green. The fruit becomes yellow when it is ripe, but the mature fruit is considered too sour and bitter. Cucumber is usually eaten raw or pickled, and certain varieties are intended for food or medicinal use (Burkill, 1985).

C. melo, the melon or muskmelon, is native to Persia and the surrounding areas, and like *C. sativus*, is now widely cultivated. Varieties of *C. melo* can be divided into smooth skinned and netted melons. In addition to their fruit, melons may be grown for their scent, seeds and oil,

or their skin, which can be dried and used as a substitute for leather. *C. melo* varieties vary greatly in both colour and flavour (Burkill, 1985). An interesting *Cucumis* species is *C. metuliferus*, the kiwano or horned melon. Native to Africa, *C. metuliferus* is also grown in Australia, New Zealand, Chile, and California. The fruit is bright orange when ripe and covered in sharp spikes, with a bright green, gelatinous flesh. Its taste has been compared to a combination of cucumber and banana. It is often eaten raw, as a snack, but may also be used in cooking (Burkill, 1985). *C. anguria*, or the West Indian gherkin, is another *Cucumis* species with a spiked fruit. It is native to Africa, but popular in Brazil, where it is used in a meat stew.

The flavour of *C. anguria* is similar to that of the cucumber (Burkill, 1985). *C. humifructus*, Southern African specie, is commonly called Aardvark cucumber or Aardvark pumpkin, because it is the only fruit eaten by the Aardvark. It is also the only *Cucumis* species with a fruit that grows underground. Another southern African species with a spiked fruit, *C. myriocarpus* or paddy melon, has become a weed in California and Australia. Unlike many *Cucumis* species, *C. myriocarpus* is toxic. It can kill livestock and has historically been used by humans as an emetic, to induce vomiting. (Burkill, 1985).

2. PHYTOCHEMICAL CONSTITUENTS OF *CUCUMIS METULIFERUS*

The plant *C. metuliferus* has several groups of secondary metabolites which account for its use as food or in the treatment of various ailments. The phytochemicals present in the fruit of *C. metuliferus* revealed the presence of useful secondary metabolites such as alkaloids, carbohydrates, cardiac glycosides, flavonoids, saponins, tannins, steroids and terpenoids (Jimam *et al*., 2011; Gotep, 2011; Usman *et al*., 2014b).

3. THERAPEUTIC EFFECTS ON VARIOUS AVIAN VIRUSES

Today, the discovery of effective natural products and alternative medicines which are able to detoxify environmental toxicants is an important scientific issue that is popular amongst people concerned about potential adverse effects of conventional medicines *Cucumis metuliferus* is one of those plants that were seriously investigated over several years and used as a prophylactic as well as a therapeutic medicinal plant. Its therapeutic effects on some avian viruses are discussed.

3. 1. Newcastle disease virus (NDV)

The poultry industry is one of the biggest and rapidly growing industries worldwide. The production of poultry meat has been rising continuously at the rate of 4% annually (Khalifa *et al*., 2013). Newcastle disease (ND) is an economically important health problem in poultry industry all around the world.

Newcastle disease virus (NDV) belongs to Paramyxovirus type 1 (APMV-1) which is an RNA virus from the genus Avulavirus of the family Paramyxoviridae (Mayo, 2002). NDV is grouped as either lentogenic, mesogenic and velogenic pathotypes based on clinical signs, virulence and mortality of infected birds (Orsi *et al*., 2009). ND deteriorates the quality of eggs, decreases the performance of birds and impairs growth (Yan *et al*., 2011).

Lentogenic strains of NDV can produce mild respiratory infection, whereas mesogenic strains can cause low mortality and neural signs and velogenic strains can result in severe mortality.

Velogenic strains may be either neurotropic velogenic NDV (NVNDV) or viscerotropic velogenic NDV (VVNDV) (Huang *et al*., 2004; Piacenti *et al*., 2006).

The only commercial control measure so far is vaccination, which does not always confer 100% immunity in birds. Vaccine breaks and failures are also a major problem. It has also been reported that vaccination itself may cause disease and reduced growth in vaccinated birds. Moreover outbreaks have been reported in vaccinated populations. Thus, there is a need to search for complementary measures. Medicinal plants have the ability to be active in preventing a variety of infectious and non-infectious diseases. One estimate revealed that 25% of all commonly used medicines have been isolated from plants (Perera and Efferth, 2012).

Currently, there are only a few drugs available for the cure of viral diseases, including acyclovir. In order to combat viruses, research efforts have been devoted to the discovery of new antiviral natural products (Mbanga *et al*., 2010; Perera and Efferth, 2012). Investigations show that local farmers in the study area claim to use *Cucumis metuliferus* fruits to treat their birds for various diseases, including Newcastle disease, by immersing the whole fruits in drinking water of birds.

Amagon *et al.*, 2012, studied the antiviral activities of *Cucumis metuliferus* fruits by determining the inhibitory activities of the virus-induced cytotoxicity of appropriate host cells. The result of this study showed a temperature and time-dependent activities of the alkaloid extract of *C. metuliferus* fruit. There was an increased protective activity of the alkaloid on the embryonated eggs against attacked by the virus with increasing temperature, and that was why the number of deaths from 4 at +4 °C was reduced to 2 at 37 °C on the 48th hours of the study. This result was similar to those some studies on the antiviral activities of some plant extracts on NDV at various temperatures (Chollom *et al.*, 2016b; Sulaiman *et al*., 2011).

HA test is used for definitive detection of viral antibody (Enzo, 2006) and the test is based on the principle of adsorbing out the cross-reacting antibodies to NDV-L antigen. Studies have shown that negative HA response observed with the higher dose of the extract means that there was no viral replication in the embryonated eggs, suggesting the absence of antibodies production in response to the viral antigen and hence antiviral activity of the extract; whereas positive HA response imply the presence of antibodies production in response to antigen as is seen with the control, where viral replication was not inhibited (Noel, 2009). This result confirmed the safety and widely use of the plant in animals and human (Noel, 2009) hence need for further work on the extract to ascertain the type of the alkaloids responsible for activities and the mechanism of action.

Furthermore, Newcastle disease is a haemorrhagic disease of birds that has a predilection for the respiratory, digestive and nervous systems, causing moderate to several deaths in susceptible flock. Nervous signs include twisted necks and paralysis while digestive symptoms include watery-greenish diarrhea. In this study, the extract of *Cucumis metuliferus* fruits suppressed these clinical signs of viral infection in chicks. Histopathological lesions of the proventriculus and ventriculus with associated necrotic haemorhages of the caecum are common in Newcastle disease. This is evident in the destruction of the adenomere and severe cellular infiltration of the proventriculus. Similarly, there is often hyperkeratinization of the ventriculus and the caecum is seen to have severe mononuclear infiltration especially into the lamina propia (**Figure 1**).

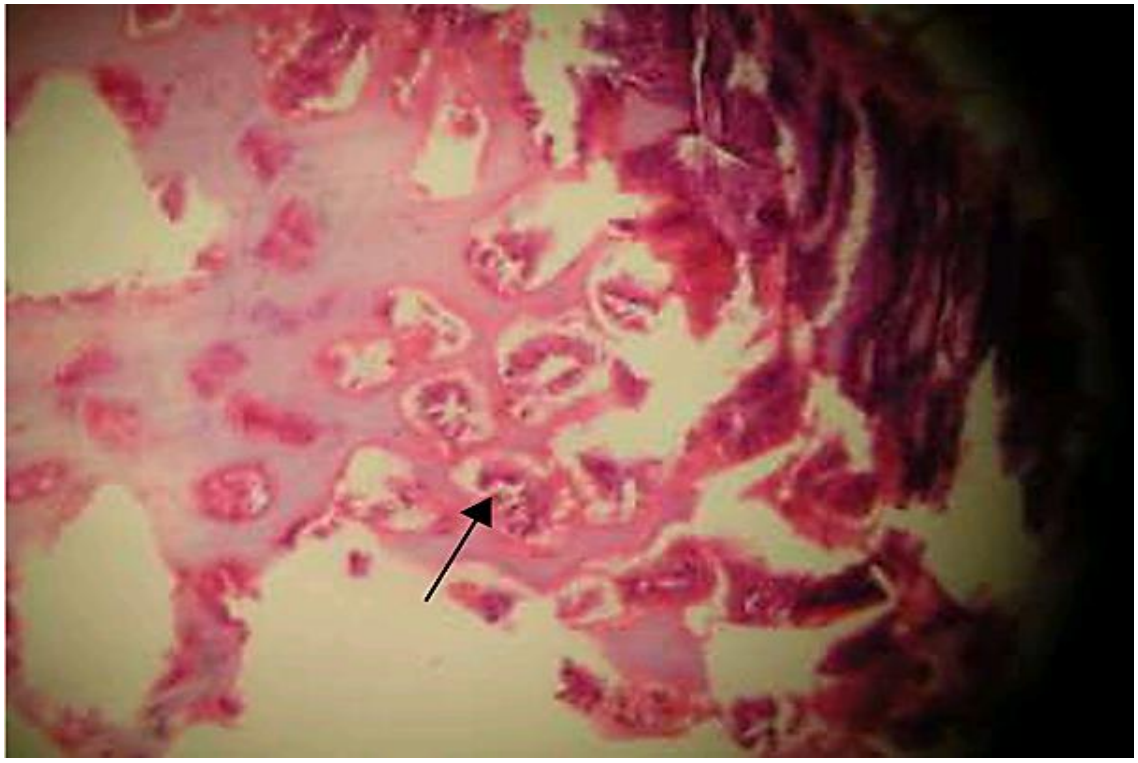

Figure 1. Ceca of animal administered the virus (Severe mononuclear infiltration into the lamina propria). Reference: (Noel *et al*., 2010)

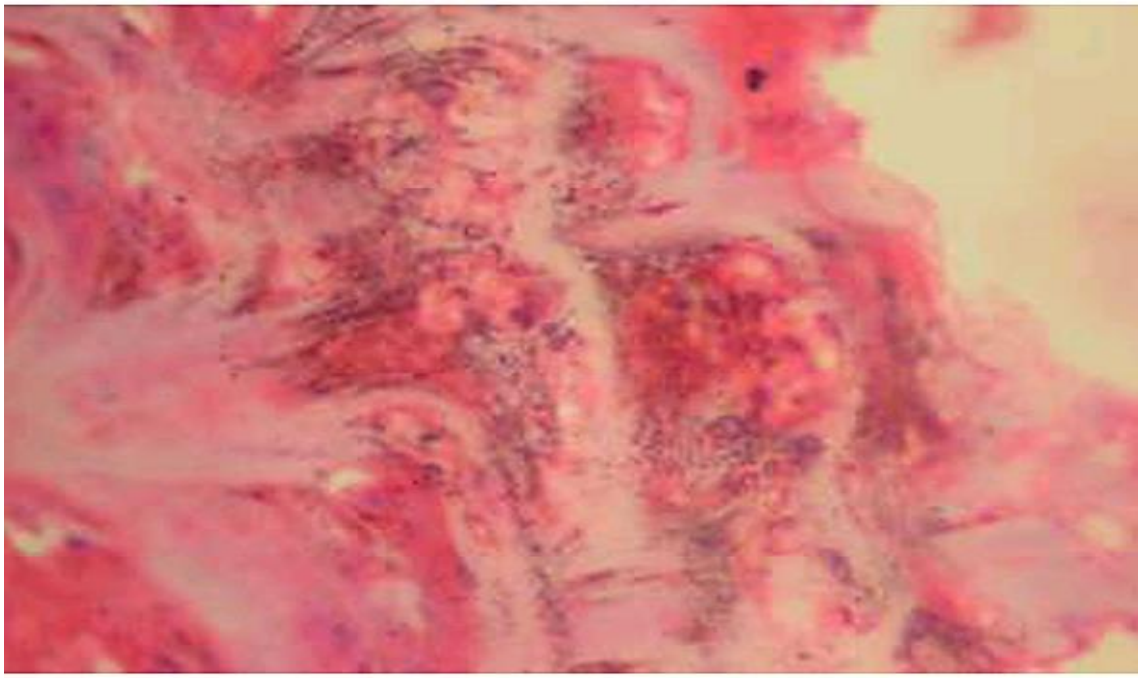

Figure 2. Ceca of animal administered with *Cucumis metuliferus* fruit extract (No visible lesion). Reference: (Noel *et al.,* 2010)

The result of this study showed that the extract reversed the haemorrhagic lesions induced by Newcastle disease virus (**Figure 2**). The results provided scientific support for the use of *Cucumis metuliferus* fruit for the management of virus associated illness.

3. 2. Infectious bursal disease virus (IBDV)

Infectious bursal disease virus (IBDV) is a viral disease that affects young birds of between two to six weeks of age with highly active bursa of fabricius (Muhammed, 1996). Human immunodeficiency virus (HIV), Newcastle disease virus (NDV) and infectious bursal disease virus (IBDV) have been shown to be similar as well as having similar pathways of entry and replication in host cells, as they all belong to the class of retroviruses (Panda, 2003; Murcia *et al*., 2009). The increase public interest in the use of alternative medicine as source of medication in human and veterinary medicine has led to good levels of interest and acceptance among health professionals (Carol *et al*., 2016; Debbiea et al., 2012; Peregoy *et al.*, 2014). Alternative antiviral obtained from plants have been documented traditionally and scientifically to have protective activities against viruses (Verma and Singh, 2008; Abonyi *et al.*, 2009; Chollom *et al.*, 2012a; Chollom *et al.*, 2012b), (**Figure 3**).

The cytotoxic and growth inhibitory effects of many plant extract have been investigated using different approaches to testing the antiviral activities of new products including herbs; (Suchman and Blair, 2007; Ayinde and Agbakwuru, 2010) with the ultimate purpose of determining the inhibition of the virus-induced cytotoxicity of appropriate host cells (McCoy and Wang, 2005).

The non-cytopathic effects of the alkaloids of *Cucumis metuliferus* fruits on the egg fibroblast observed was in accordance to previously established safety margin of the oral dose of 5000 mg/kg of the crude extract in laboratory animals (Cardoso *et al*., 2000). The safety and widely used of the fruit of this plant for its antiviral activities have been documented (Wannang *et al.*, 2010). The toxicity result of this study was similar to toxicity study of the flavonoids extract of the plant's fruits conducted by Amagon *et al*., 2012, and Wannang *et al.*, 2008, and also reports on other herbs using embryonated eggs (Amagon *et al.*, 2012). Absence of cytopathic effect on the fibroblast cell of the eggs when exposed to the virus and the alkaloids was an indication of the activity of the alkaloids at these doses against the known structural changes that occur in host cells due to viral invasion. It is a known fact that when virus invades host cells, the infecting virus either impacts cytopathic effects by lysis of the host cells or killing the cell without lysis through inhibiting its reproductive activities (Wafaa *et al.*, 2007).

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The alkaloids of *C. metuliferus* were able to inhibit the replication of IBDV and hence its damaging effects on the chicken embryo fibroblast cells at higher concentration, while at lower concentration, the effect of the extract does not inhibit the growth of the virus, thereby increasing its damaging effects on the chicken embryo cells. In cases where no CPE was evident, the virus was assumed to be completely inactivated or inhibited (Wannang *et al.*, 2008). The result of the study showed that the alkaloids extracted from *C. metuliferus* fruit have some good margin of safety and antiviral activities on IBDV compared to the control.

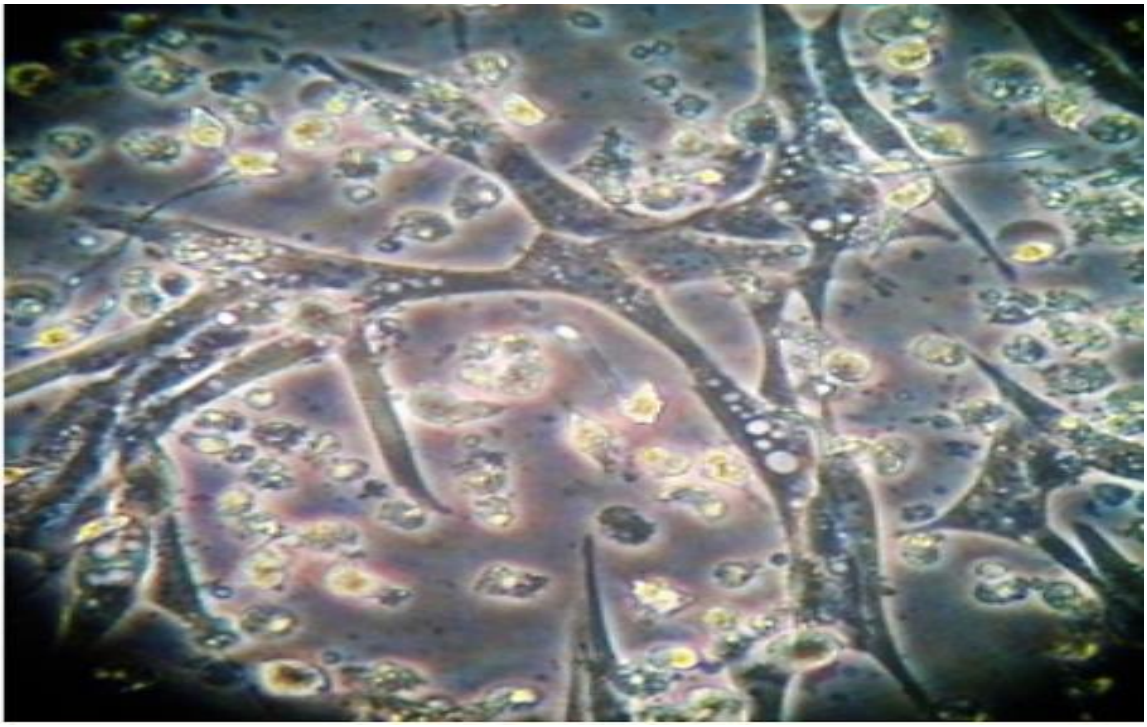

Figure 3. Chicken embryo fibroblast (CEF) cell line showing CPE caused by IBD Virus. Reference; (Hari Mohan Saxena and Pushpinder Kaur, 2020)

3. 3. Hepatitis B Virus (HBV)

Hepatitis can be described as a diffuse inflammatory disease of the liver which may be associated with hepatocellular necrosis affecting the acini, and are caused by different types of viruses including hepatitis B virus. This virus has surface antigens that are labeled HBsAg, HBcAg, and HBeAg (Bosch and Abaldes, 2005). Replication of HBV has been shown to be sorely in the liver, perhaps other extra-hepatic replication sites also exist (Friedman and Keefe, 2004).

Studies have shown that treatment of liver disease using orthodox approach has been so difficult, and herbal preparations have been useful for the treatment of liver disorders (Somasundaram *et al.*, 2010). The need for the development of an efficient hepatoprotective drug from the natural resource is therefore a necessity (Tandon *et al.*, 2008). The use of herbs as antiviral agents have been documented scientifically (Abonyi *et al.*, 2009). These authors further stated that alkaloids isolated from these plants have been proven to have antiviral properties. Though, the antiviral properties of the ethanolic crude extract of *C. metuliferus* fruit have been reported (Noel *et al.*, 2009), not much have been documented on the activities of the alkaloidal content of the plant on hepatitis B virus.

The results on the effect of the alkaloids of *C. metuliferus* fruit on the biochemical parameters of hepatitis B virus-induced liver damage showed significant dependent decrease in the levels of alkaline phosphatase (ALP) and alanine aminotransferase (ALT). Previous studies have shown that changes in serum enzymes concentration may be a signal of hepatic pathological process (Benjamin, 1978).

It has been reported that both ALT and AST are located in the cytoplasm and mitochondria of liver cells, and also in cells of the heart, skeletal muscles, kidney and brain (Wannang *et al*., 2007). These authors further stated that the activities of ALT outside the liver are low and hence this is considered more specific for hepatocellular damage. ALP has been reported to be widely distributed in the body with significant activities in the liver, gastrointestinal tract, bone marrow and placenta (Wannang *et al*., 2007). Studies have shown that the mechanism underlying drug and chemically induced hepatotoxicity is free radicals activities through lipid peroxidation and oxidative stress (Diazani *et al.*, 1991). The observed dosed- dependent decrease in the levels of enzymes concentrations is suggestive of the protective effect of the administered alkaloids in the animals, which could be by antioxidation through the process of mopping up or scavenging of free radicals generated during hepatic injury (Abdullah and Al-Assaf, 2013; Barbaste *et al.* 2002).

4. CONCLUSION

Cucumis metuliferus fruits belong to the family Cucurbitaceae, and are largely consumed as raw food and for medicinal purposes all over the world. It is the potential source of bioactive secondary metabolites. Pharmacological and phytochemical studies of *Cucumis metuliferus* fruits have received much interest because of their flavonoid and alkaloid constituents. While going through the literature it is shown *Cucumis metuliferus* fruits contain adequate amount of beneficial bioactive compounds for the maintenance of health of avians. However, there is need of utilization of these bioactive compounds from different edible and non-edible part of *Cucumis metuliferus* fruits as alternative to antivirals with no adverse effects. It could be a possible natural mode of treatment for different poultry viral infections.

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References

[1] Abdullah, H. Al-Assaf. Hepatoprotective and antioxidant effect of corosolic acid on carbon tetrachloride induced hepatotoxicity. *African Journal of Pharmacy and Pharmacology* 7(12) (2013) 673-678

[2] Abonyi D.O., Adikwu M.U., Esimone C.O., Ibezim E.C. Plants as Sources of Antiviral Agents. *African Journal of Biotechnology*, 899 (17) (2009) 3989-3994

[3] Aggarwal B.B., Sundaram C., Malani N. and Ichikawa, H. Curcumin, "the Indian Solid Gold" *Adv. Exp. Med. Biol*. 595 (2007) 1-75

[4] Alawa C.B.I., Adamu, A.M., Gefu J.O., Ajanusi O.J., Abdu P.A., Jagun A.G., Lamidi O.S., Oni O.O. Ethnoveterinary practices in Nigeria: Survey of plants used as anthelmintics. *Vom J. Vet. Sci*. 5(1) (2008) 2-11

[5] Amagon K.I., Wannang N.N., Iliya H.A., Ior L.D., Chris-Otubor G.O. Flavonoids Extracted from Fruit Pulp of Cucumis metuliferus Have Antiviral Properties. *Brit. J. Pharm. Res*. 2(4) (2012) 249-258

[6] Ayinde B.A., Agbakwuru U. Cytotoxic and growth inhibitory effects of the methanol extract of *Struchium sparganophora Ktze* (Asteraceae) leaves. *Phcog Mag*. 6(24) (2010) 293-297

[7] Barbaste M., Berkee B., Dumas M., Soulet S., Delaunay J.C., Castagnino C., Arnaudinaud V., Cheeze C., Vercauteren J. Dietary antioxidants, peroxidation and cardiovascular risks. *J. Nutr. Health Aging*, 6 (2002) 209-223

[8] Beloin N., Gbeassor M., Akpagana K., Hudson J., De Soussa K., Koumaglo K., Arnason, J. T. Ethnomedicinal uses of *Momordica charantia* (Cucurbitaceae) in Togo and relation to its phytochemistry and biological activity. *J. Ethnopharmacol.* 96 (1–2) (2005) 49-55

[9] Benjamin M.N. Outline of veterinary clinical pathology, University press, Iowa, USA. (1978) 229-232

[10] Benzioni A., Mendlinger A., Ventura M., Huyskens S. Germination, Fruits Development, Yield and Post-Harvest Characteristic of Cucumismetuliferus. In: Janick J, Simon JE, editors. New York: New Crops Wiley; (1993) 553-755

[11] Bosch J., Abaldes J.G. Variceal Bleeding: Pharmacological Therapy. *Digestive Disease*, 23 (2005) 18-29

[12] Burkill, H.M. *Useful Plants of West Tropical Africa.* Vol.1, 2nd Ed. Royal Botanic Gardens, London. (1985) 570-605

[13] Camporese A., Balick M.J., Arvigo R. Esposito, R.G., Morsellino, N., De Simone, F., Tubaro, A. Screening of antibacterial activity of medicinal plants from Belize (Central America). *J. Ethnopharmacol*. 87 (2003) 103-107

[14] T.C. Cardoso, P. Rahal, D. Pilz, M. C. B. Teixeira & C. W. Arns (2000) Replication of classical infectious bursal disease virus in the chicken embryo related cell line. *Avian Pathology*, 29:3, 213-217, DOI: 10.1080/03079450050045468

[15] Carol A.W., Kent S., Jon B., Alexander K., Alexandra G., Tierney K., *et al*. Attitudes toward Chiropractic: A Survey of Canadian Obstetricians. *Evid-Based Complement*. & *Altern. Med*. 21(2) (2016) 92-104

[16] Chollom S.C, Agada G.O, Bot D.Y., Okolo M.O., Dantong D.D., Choji T.P. Phytochemical analysis and antiviral potential of aqueous leaf extract of *Psidium guajava* against Newcastle disease virus in vivo. *J. Appl. Pharmaceut. Sci*. 2 (2012b) 45-9

[17] Chollom S.C., Olawuyi A.K., Danjuma L.D., Nanbol L.D., Makinde I.O., Hashimu G.A. Antiviral potential of aqueous extracts of some parts of Momordica balsamina plant against Newcastle disease virus. *J. Adv. Pharm. Educ. Res*. (2012a) 82-92

[18] Debbiea S., Graeme L., Pierrec D., Williamson E., Kelvin C. Pharmacovigilance of herbal medicine. *Journal of Ethnopharmacol*. 140 (2012) 513–518

[19] Devi B.P., Boominathan R., Mandal S.C. Evaluation of antipyretic potential of *Cleome viscose* Linn. (Capparidaceae) extract in rats. *J. Ethnopharmacol*. 87 (2003) 11-13

[20] Diazani M.U., Muzia G., Biocca M.E., Canuto R.A. Lipid peroxidation in Fatty Liver-Induced by Caffeine in Rats. *International Journal of Tissue Reaction*, 13 (1991) 79-85.

[21] Erdogrul O.T. Antibacterial activity of some plant extracts used in folk medicine. *Pharm. Microbiol*. 40 (2002) 269-273

[22] Fabry W., Okemo P.O., Ansorg R. Antibacterial activity of East African medicinal plants. *J. Ethnopharmacol*. 60 (1998) 79-84

[23] Friedman L.S., Keefe E.B. Handbook of Liver Disease. Chrchhill Livingstone, Edinburgh; (2004) 17-19

[24] Gedif T., Hahn H.J. The use of medicinal plants in self-care in rural central Ethiopia. *J. Ethnopharmacol*. 87 (2003) 155-161

[25] Geidam Y.A., Ambali A.G., Onyeyili P.A. Preliminary phytochemical and antibacterial evaluation of crude aqueous extract of *Psidium guajava* leaf. *J. Appl. Sci.* 7(4) (2007) 511-514

[26] Gotep, J. Glycosides fraction extracted from fruit pulp of Cucumis metuliferus E. Meyer has antihyperglycemic effect in rats with alloxaninduced diabetes. *J. Nat. Pharm.* 2 (2011) 48-51

[27] Guarrere P.M., Forti G., Marignoli S. Ethnobotanical and ethnomedicinal uses of plants in the district of Acquapendente (Latium, Central Italy). *J. Ethnopharmacol*. 96 (2005) 429-444

[28] Gupta, M.P, Solís, P.N., Calderón, A.I., Guinneau-Sinclair, F., Correa, M., Galdames, C., Guerra, C., Espinosa, A., Alvenda, G.I., Robles, G., Ocampo, R. Medical ethnobotany of the Teribes of Bocas del Toro, Panama. *J. Ethnopharmacol*. 96 (2005) 389-401

[29] Hamill F.A., Apio S., Mubiru N.K., Bukenya- Ziraba R., Mosango M., Maganyi O.W., Soejarto D.D. Traditional herbal drugs of Southern Uganda, II: literature analysis and antimicrobial assays. *J. Ethnopharmacol*. 84 (2003) 57-78

[30] Hari Mohan Saxena, Pushpinder Kaur. Insights into the Identity of the Putative Molecular Target of Infectious Bursal Disease Virus on Chicken Bursal Cells. *Acta Scientific Microbiology*, 3 (2020) 11: 61-73

[31] Harsha V.H., Hebbar S.S., Shripathi V., Hegde G.R. Ethnomedicobotany of Uttara Kannada district in Karnataka, India plants in treatment of skin diseases. *J. Ethnopharmacol*. 84 (2003) 37-40

[32] Hashish, M.N., Gomaa, N.F. The inhibitory effects of garlic (*Allium sativa*) on growth of some microorganisms. *J. Egypt. Pub. Hlth. Assoc*. 78(5-6) (2003) 361-72

[33] Hernández T., Canales M., Avila J.G., Duran A., Caballero, J., Romo de Vivar, A., Lira A. Ethnobotany and antibacterial activity of some plants used in traditional medicine of Zapotitlán de las Alinas, Puebla (Mexico). *J. Ethnopharmacol*. 88 (2003) 81-188

[34] Huang Z., Panda A., Elankumaran S., Govindarajan D., Rockemann D.D., Samal S.K.The haemaglutinin-neuraminidase protein of Newcastle disease virus determines tropism and virulence. *Journal of Virology*, 78 (2004) 4176-4184

[35] Iwalokun B.A., Ogunledun A., Ogbolu D.O., Bamiro S.B., Jimi- Omojola J. *In-vitro* antimicrobial properties of aqueous garlic extract multi-drug resistant bacteria and *Candida* species from Nigeria. *J. Med. Food*, 7(3) (2004) 327-333

[36] Jabbar A., Akhtar M.S., Muhammed G. and Lateef M. Possible role of ethnoveterinary medicine in poverty reduction in Pakistan: use of botanical anthelmintics as an example. *J. Agric. Soc. Sci.*, 1(2) (2005) 187-195

[37] Jimam N.S., Wannang N.N., Anuka J.A., Omale S., Falang K.D., Adolong A.A. Histopathologic Effects of *C. metuliferus* EMey (Cucurbitaceae) Fruits in Albino Rats. *Intern. J. Pharm. Sci. Res*. 2(8) (2011) 2190-2194

[38] La Cour B., Mølgaard P., Yi, Z. Traditional Chinese medicine in treatment of hyperlipidaemia. *J. Ethnopharmacol*. 46 (1995) 125-129

[39] Lin J., Opoku A.R., Geheeb-Keller M., Hutchings A.D., Terblanche S.E., Jäger A.K., van Staden. Preliminary screening of some traditional Zulu medicinal plants for anti-inflammatory and anti-microbial activities. *J. Ethnopharmacol*. 68 (1999) 267-274

[40] Matu E.N., Van Staden J. Antibacterial and anti-inflammatory activities of some plants used for medicinal purposes in Kenya. *J. Ethnopharmacol*. 87 (2003) 35-41

[41] Mathias E., McCorkle C.M. Traditional Livestock healers. *Revue Scientifique et Technique* 23(1) (2004) 277-284

[42] Mayo M.A. A summary of taxonomic changes recently approved by ICTV. *Archives of Virology*, 147 (2002) 1655-1663

[43] Mbanga J., Mangoma, N., Saidi, B. An evaluation of the antimicrobial activities of Aloe barbadensis, A. chabaudii and A. arborescens leaf extracts used in folklore veterinary medicine in Zimbabwe. *Journal of Animal and Veterinary Advancement*, 9 (2010) 2918-2923

[44] McCoy M.H., Wang E. Use of electric cell-substrate impedance sensing as a tool for quantifying cytopathic effect in influenza A virus infected MDCK cells in real-time. *J. Virol. Methods*, 130 (2005) 157-61

[45] Merken H.M., Merken C.D., Beecher G.R. Kinetics method for the quantitation of anthocyanidins, flavonols, and flavones in foods. *J. Agric. Food Chem*. 49 (2001) 2727–2732

[46] Muhammed I, Anwar MS, Yaqup MT. Failure of Vaccines to Control Infectious Bursal Disease in Commercial Poultry. *Pakistan Veterinary Journal*, 16 (1996) 119-21

[47] Murcia P.W., Donachie M., Palmarini M. Viral Pathogens of Domestic Animals and their Impact on Biology, *Medicine and Agriculture. Encyclopedia of Microbiology*, (2009) 805-819

[48] Mwale M., Bhebhe E., Chimonyo M., Halimani T.E. Use of herbal plants in poultry health management in the Mushagashe small-scale commercial farming area in Zimbabwe. *The Intern. J. Appl. Res. Vet. Med*. 3(2) (2005) 163-170.

[49] Nandagopalan V., Anand S.P., Lakshmi prabha A., Selvakumar U. and Doss, A. An ethnobotanical Study in the Pudukkottai District, South India. *Asian J. Exp. Biol. Sci*. 2(3) (2011) 412- 421.

[50] Noel N., Wannang Helen O., Kwanashie, and Samuel O. Ede. Antiviral Activity of the Fruit Extract of *Cucumis metuliferus* E. Meye (Curcubitaceae) in Chicks. *African J. of Basic & Appl. Sci*. 2 (3-4) (2010) 89-93

[51] Noel N.W., Simeon O., Steven S.G., Nanloh S.J., Maxwell L.D., Elekwechi I., *et al*. Evaluation of the antiviral properties of the ethanolic extract of the fruit pulp of *Cucumis metuliferus E*. Meye (Curcubitaceae). *Niger. J. Sci. Res*. 8 (2009) 55-59

[52] Ofukwu R.A., Ayoola A. and Akwuobu C.A. Medicinal plants used in the treatment of tuberculosis in humans and animals by Idoma tribe of North Central Nigeria. *Nig. Vet. J.* 29(2) (2008) 25-30

[53] Orsi M.A., Doretto J.L., Reischak D., Da Silva L.H., Spilki D.R., Buzinaro M.G., Arns, C.W. 2009. Newcastle disease virus vaccine strains: immunogenicity is not influenced by ICPI. *Brazilian Journal of Poultry Science*, 11 (2003) 129-133

[54] Panda A. Role of Haemagglutination-Nueraminidase protein in Newcastle Disease Virus Pathogenesis. PhD Dissertation Submitted to the Postgraduate School, University of Maryland. (2003)

[55] Perera C. and Efferth T. Antiviral medicinal herbs and phytochemicals. *Pharmacognosy Journal*, 3 (2012) 45-48

[56] Peregoy J.A., Clarke T.C., Jones L.I., Barbara J.S., Richard L.N. Regional variation in use of complementary health approaches by U.S. adults. NCHS data brief, no 146. Hyattsville, MD: Nat Cent Health Stat. (2014)

[57] Piacenti A.M., King D.J., Seal B.S., Zhang J. And Brown C.C. Pathogenesis of Newcastle disease in commercial and specific pathogen free turkeys experimentally infected with isolates of different virulence. *Veterinary Pathology*, 43 (2006) 168-178

[58] Rabe T. and van Staden J. Antibacterial activity of South African plants used for medicinal purposes. *J. Ethnopharmacol.* 56 (1997) 81- 87

[59] Ritch-Krc E.M., Thomas S., Turner N.J. and Towers G.H.N. Carrier herbal medicine: traditional and contemporary plant use. *J. Ethnopharmacol.* 52 (1996) 85-94

[60] Roodt V. Trees and Shrubs of the Okavango Delta. Shell Field Guide Series. (1998) 41-49

[61] Schillhorn van Veen T.W. Sense or nonsense? Traditional methods of animal disease prevention and control in the African Savannah. In *Ethnoveterinary Research and Development* (C. M. McCorkle, E. Mathias and T. W. Schillhorn van Veen, eds. Intermediate Technology Development Group Pub. London. (1996) 25-36

[62] Semple S.J., Reynolds G.D., O'Leary M.C., Flower, R.L.P. Screening of Australian medicinal plants for antiviral activity. *J. Ethnopharmacol.*, 60 (1998) 163- 172.

[63] Silva N.C.C., Fernandes Jr, A. Biological properties of medicinal plants: a review of their antimicrobial activity. *The J. Venomous Anim. Toxins Including Trop. Dis*. 16(3) (2010) 402-413

[64] Sinclair, S. Chinese herbs: a clinical review of Astragalus, Ligusticum, and Schizandrae. *Alternative Medicine Review*, 3 (1998) 338–344

[65] Sodipo O.A., Ojo, M., Nwafor P.A. The effects of methanolic stem bark extract of *Paustinystalia yohimbe* Pierre on rat's gastrointestinal tract. *Nig. J. Exp. Appl. Biol*. 6(2) (2005) 157-160

[66] Somasundaram A., Karthikeyan R., Velmurugan V., Dhandapani B., Raja M. Evaluation of hepatoprotective activity of *Kyllinganemoralis* (Hutch &Dalz) rhizomes. *J. Ethnopharmacol*. 127 (2010) 555

[67] Suchman E., Blair C. Cytopathic Effects of Viruses Protocols. *American Society for Microbio*logy (2007)

[68] Sulaiman L.K., Oladele O.A., Shittu I.A., Emikpe B.O., Oladokun A.T., Meseko C.A. In-vivo Evaluation of the Antiviral Activity of Methanolic Root-Bark Extract of the African Baobab (*Adansonia Digitata Lin*). *Afr. J. Biotech*. 10 (2011) 4256-4258

[69] Tandon V.R., Khajuria V., Kapoor B., Kour D., Gupta S. Hepato-protective activity of Vitexnegundo leaf extract against anti-tubercular drugs induced hepatotoxicity, *Fitoterapia*, 79 (2008) 533

[70] Usman J.G. Phytochemical Screening and Antibacterial Effects of *Cucumis Metuliferus* (Jelly Melon) E. Mey. Ex Naudin (Cucurbitaceae) Fruits against Fowl Typhoid. A Dissertation Submitted to the School of Postgraduate Studies, University of Maiduguri, In Partial Fulfilment of the Requirement for the Degree of Master of Science in Pharmacology. (2014) 155 pp.

[71] Usman, J.G., Sodipo, O.A., Sandabe, U.K. Phytochemical screening and acute toxicity study of *Cucumis metuliferus* E. Mey. Ex. Naudin fruit extract in cockerels. *Intern. J. Phytomed*. 6(2) (2014b) 243-247

[72] Verma S., Singh S.P. Current and future status of herbal medicines-Review. *Veterinary World*, 1(11) (2008) 347-350

[73] Wafaa A.H., Howaida I.A., Hassan A., El-Safty M.M. Chemical Composition and 'InVitro' Antiviral Activity of *Azadirachta Indica* A. Juss (Neem) Leaves and Fruits against Newcastle Disease Virus and Infectious Bursal Disease Virus. *Australian. J. Basic Applied Sci*., 1 (2007) 801-812

[74] Wannang N.N., Jimam N.S., Omale S., Dapar M.L., Gyang S.S., Aguiyi J.C. Effects of *Cucumis metuliferus* Fruits on Enzymes and Haematological Parameters in Albino Rats. *African J. of Biotech*. 6 (22) (2007) 2515-2518

[75] Wannang N.N., Jimam N.S., Gyang S.S., Bukar B.B., Gotom S. Effects of *Cucumis metuliferus* E Mey. Ex Naud (Cucurbitaceae) fruit extract on some male reproductive parameters in adult rats. *Afr. J. Pharm. Pharmacol*. 2(3) (2008) 048-051

[76] Wannang N.N., Kwanashe H.O., Ede S. Antiviral activity of the Fruit Extract of *Cucumis metuliferus* E Meye (Curcubitaceae) in Chicks. *African J. of Basic and Applied Sci*. 2(3-4) (2010) 89-93

[77] Mikołaj Kostryco, Mirosława Chwil. Biologically active compounds in Agrimoni eupatoria L. and their therapeutic effects. *World Scientific News* 89 (2017) 90-97

[78] Yan Z., Du, Y., Zhao Q., Fan R., Guo W., Ma R., Wang X., Zhu R. Mucosal immune responses against live Newcastle disease vaccine in immunosuppressed chickens. *Pakistan Veterinary Journal*, 31 (2011) 280-286

[79] Yeşilada E., Honda G., Sezik, E., Tabata M., Fujita T., Tanaka T., Takeda Y., Takaishi Y. Traditional medicine in Turkey. V. Folk medicine in the inner Taurus Mountains. *J. Ethnopharmacol*. 46 (1995) 133-152

[80] Zheng W. and Wang S.Y. Antioxidant activity and phenolic compounds in selected herbs. *J. Agric. Food. Chem*. 49 (2001) 5165-5170