Journal of Medicinal Plants Research Vol. 5(22), pp. 5324-5330, 16 October, 2011
Available online at http://www.academicjournals.org/JMPR
ISSN 1996-0875 ©2011 Academic Journals

Review

Juglone: A therapeutic phytochemical from *Juglans regia* L.

Ajay Thakur

Tissue Culture Discipline, Forest Research Institute, Dehradun, Uttarakhand, India 248006, India.
E-mail: mithoojorhat@yahoo.co.in.

Accepted 14 June, 2011

***Juglans regia* L. is a monoecious, heterodichogamous, deciduous tree species valued for its high-quality timber as well as its nuts. It belongs to the family Juglandaceae. Though, it is native to Central Asia, India, Nepal China and some part of Europe, it is being grown commercially in the USA, France, Italy and Spain for nut production. The nuts and plant parts of *J. regia* contain the aromatic secondary metabolite juglone ($C_{10}H_6O_3$) (1, 4 – naptha quinone, 5 hydroxy – 8Cl). Juglone is a well-known allelopathic agent and being used in commercial hair dye and also has therapeutic properties. Juglone is commercially extracted from the husks of walnuts, but fresh leaves of *J. regia* contain significant amounts of juglone (up to 0.5 / 100 g dry weight) to be a good source of the chemical. Juglone is understudy for anti-carcinogenic effects. In human intestinal neoplasia juglone checked multiplicity of tumour cells and is also a strong inhibitor of peptidyl-prolyl isomerase Pin1 which is overexpressed in several types of cancer affected cells. Juglone increases efficacy of anti cancer drugs as well.**

Key words: Phytochemical, medicinal, anticarcinogenic, antitumor, allelopathic.

INTRODUCTION

Juglans regia L. is a monoecious, heterodichogamous, deciduous tree species valued for its high-quality timber as well as its nuts (Malvolti et al., 1995). It belongs to the family Juglandaceae and the genus *Juglans.* The natural range of *J. regia* extends from China in the east to Turkey in the west and from Kazakhstan in the north to temperate regions of India and Nepal in the south. *J. regia* is grown commercially in China, the USA (California), France, India, Italy and Spain for nut production. This species has an aromatic phytochemical Juglone ($C_{10}H_6O_3$; 1, 4 – naptha quinone, 5 hydroxy – 8Cl) found in all parts (Harborne, 1988) (Figure 1). This chemical is one of the oldest known allelopathic compounds in the history of cultivation and is also used as an active ingredient in herbal remedies and commercial dye (Erdemoglu et al., 2003; Harborne, 1988). Juglone has been reported as an important therapeutic phytochemical and is under investigation for its reported carcinogenic/anti-carcinogenic effects (Sugi et al., 1998; Segura-Aguilar et al., 1992).

THE SPECIES: *JUGLANS REGIA* L.

The Juglandaceae is a large family containing two major clades, two tribes, two sub-tribes, seven genera and approximately 60 deciduous and monoecious species. In addition to the genus *Juglans* L. (walnuts), the family includes *Carya* Nutt. (pecans and hickories), *Pterocarya* Kunth. (wingnuts), *Platycarya* Sieb. and Zucc., *Engelhardia* Lesche. *ex* Blume, *Alfaroa* Standl., and *Oremunnea* Oerst. (Manning, 1978; Polunin, 1977; Manos and Stone, 2001). There are 20 species in the genus *Juglans*, grouped in four subgenera: *Juglans* Mann., *Trachycaryon* Dode *ex* Mann., *Cardiocaryon* Dode, and *Rhysocaryon* Dode (Manning, 1978). *J. regia* is the sole species within the subgenus *Juglans*, and is characterised by a four-celled nut, a husk which separates from the nut at maturity, and seedlings which exhibit two rows of scale buds immediately above the cotyledons and below the spirally-arranged compound leaves (Figure 2). *J. regia* is medium to large tree (up to 30 m tall in natural conditions) with a spreading crown. The leaves are compound and composed of 7 to 9 leaflets, which have prominent, herring-bone venation. Leaflets are ovate, with pointed tips and smooth margins (Polunin, 1977). *J. regia* is monoecious and hetero-dichogamous, bearing male and female reproductive organs in separate flowers on the same tree (Polunin, 1977; Gleeson, 1982).

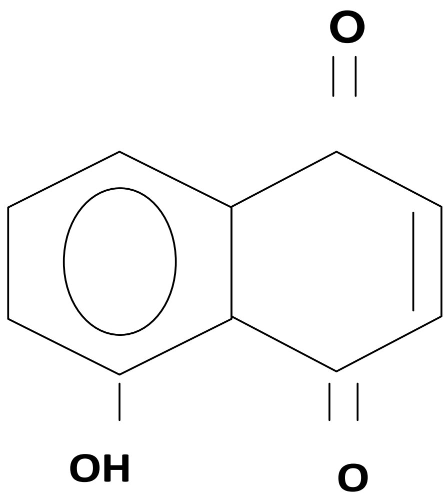

Figure 1. Structural formula of juglone.

Catkins (male inflorescences) are borne laterally on one-year-old wood, and pistillate flowers are borne terminally or laterally on the current season's wood in spikes of typically 2 to 3 flowers. Pistillate flowers lack visible sepals and petals, and are pubescent, small and green. The female flowers have merely an ovary with a large, feathery stigma. The ovary wall is fused to bract or involucre tissue and the outer ovary wall plus the involucre become the fleshy husk of the fruit. Male flowers generally appear later in life than female flowers (Polunin, 1977; Westwood, 1977; Jackson and McNeil, 1999). *J. regia* is anemophillous and protandrous. Though most walnuts are self-fertile, female flowers receive pollen from different plants due to the different timing of the functions of male and female flowers. Pollen is released 10 to 12 days after bud break (Jackson and McNeil, 1999). Nuts develop in groups of one to three on shoot tips. A green, fleshy husk surrounds the nut, which splits irregularly at maturity. The husk is easily separated from the nutshell. The shell is rough, wrinkled or furrowed, and thin. Nuts are ovoid to round, 1.25 to 5.00 cm in diameter, and contain two kernels separated by a thin, papery central plate extending from the inner layer of the shell. Nut production starts usually at age 4 to 6 years but commercial production starts after trees reach 10 years of age. Walnuts mature 4.5 to 5 months after flowering, and are harvested in September-October (Polunin, 1977; Westwood, 1977; Jackson and McNeil, 1999).

Distribution of Juglans regia

J. regia is one of the oldest cultivated nut-producing species in the history of mankind. Because of its quality nuts it is cultivated in most of the temperate part of the northern Hemisphere. In some places, namely central Asia and its periphery, the Balkan regions of Europe and the Indian sub-continent, it still grows in the wild (Gamble, 1902; Polunin, 1977; Jackson and McNeil, 1999). In other areas, it is either cultivated following deliberate introduction or is only available in cultivated form because it has been lost in the wild.

Natural range

J. regia is reported to grow in the wild across 19 countries on the Asian continent (Figure 3). It occurs from Turkey and Iraq (Kurdistan) in the west, countries around the Caspian Sea (Azerbaijan, Armenia, Russia, and Georgia, Iran and Turkmenistan) and further north (Uzbekistan, Kyrgyzstan, Tajikistan and Kazakstan) to the north-eastern Xinjiang region of China. Southwards it occurs in Afghanistan and extends south to the Karakoram and Himalayan mountain ranges of Pakistan, India, Nepal and Bhutan, and finally reaches its south-eastern limit in Bangladesh, the hills of upper Myanmar (Burma), and southern China (Gamble, 1902; Zohary, 1993; Kolov, 1998; Hemery, 2000; Thakur 2006). It disappeared from the south east of Europe and south west Turkey during the last glaciation and reappeared in the Balkans and west Turkey in the latter part of second millennium BC. Some authors consider that this re-appearance was not the result of a post-glacial migration but of movement by humans (Zohary, 1993). However, it is believed that *J. regia* is native to Greece and the Balkan Peninsula (Jalas and Suominen, 1976; Polunin, 1977; Tutin et al., 1993).

Rest of the world

Though the evidence of charred walnut in Europe dates from the Iron Age, but the Romans marches in Europe also has some considerable role in widespread distribution of *J. regia* in Europe mostly through the cultivation in conquered regions. The high pollen counts present 1000 years before present (BP) reflect the widespread cultivation and planting of walnut across most of Europe (Huntley and Birks, 1983). Nuts were used for food, and the wood was used for gunstocks and quality furniture. Alternative tropical woods were largely unknown, and so it was propagated in most of southern Europe and later in the UK. Artifacts made from *J. regia* have been found at Roman sites in London (Roach, 1985). English settlers took the species to North America and the USA is now one of the biggest producers of *J. regia* nuts, mainly in the state of California (Westwood, 1977).

JUGLONE

Juglone ($C_{10}H_6O_3$, 1, 4 – naptha quinone, 5 hydroxy –8Cl) is an aromatic compound reported to be found in

Figure 2. *Juglans regia* L.1, leaves on twig; 2, male catkins on twig; 3, female flower; 4, lateral section of young female flower; 5, male flower and anther; 6, scale; 7, fruit; 8, transverse section of fruit (Reproduced from Townsend, 1980).

Juglans regia, *Juglans nigra*, *Juglans cineraria* and in other species of the family Juglandaceae such as *Carya olivivaeformis*, *Pterocarya caucarica* and *Pterocarya stemoptera* (Thomson, 1957). In *J. regia*, it is reported to be present in all plant parts including the leaves, roots, stem, branches and nuts. Juglone is present in significant amounts (0.5 g / 100 g dry weight) in fresh leaves of *J. regia* (Harborne, 1988; Gîrzu et al., 1998), though plant to plant variation of juglone in fresh leaves was in the range of 13.1 to 1556.0 mg / 100 g dry weight on the basis of 1121 trees leaf samples (Thakur and Cahallan, 2011).

Chemical description

Chemical name: 1, 4 – napthaquinone, 5 hydroxy-(8CI); Common name: juglone

Phyto-medicinal uses of juglone

Juglone has a wide array of uses in daily life and is used as natural dye in the wool and hair dyeing industries (Harborne, 1988). It is reported to have medicinal properties against ring worm, fungal, bacterial and viral infections and is used as cure for heat stroke (Erdemoglu et al., 2003). Juglone inhibits the growth of oral cariogenic bacteria (*Streptococcus mutans* and *Streptococcus sanguis*) and periodontal pathogens (*Porphyromonas gingivalis* and *Prevotella intermedia*) (Cai et al., 2000). It is also reported to have a purgative action and in finely powdered form it is an effective

Figure 3. Distribution of *Juglans regia* in natual range.

sternutator (Erdemoglu et al., 2003). It has been found to be nematicidal to root-knot nematodes (Dama, 2002), and in the USA it is reported to be used for fish poisoning (Thomson, 1957; Westfall et al., 1961).

Toxicity of juglone

Toxicity of juglone to plants

Walnut has been reported to have allelopathic effects on other nearby plants since the time of Pliny (23 to 79 AD) (Thomson, 1957). In the early 20th century, Massey (1925) reported the allelopathic effect of walnut on tomato and alfalfa and Schneiderhan (1927) reported similar effects on closely planted apple trees (Harborne, 1988). Initially, toxin exudates from roots were considered to be responsible for this allelopathic effect. Later, Bode (1958) reported that the upper part of the tree (leaf, branch and stems) were also responsible for toxin exudation. He also reported that the toxic form of juglone only appeared after oxidation in soils. So, juglone is potentially an environmentally toxic substance, but in soil it has limited movement as it is poorly soluble in water and may break down in two months. Juglone contents in soils (Table 1) show seasonal variation; high in spring, declined during summer and were high again in autumn (Scisciolo et al., 1990).

Reitveld (1983) studied the juglone sensitivity to seed germination, radical growth and shoot elongation of 16 herbs, shrubs and trees. Seed germination of six out of 14 tested species, radical elongation of 11 out of 15 tested species and shoot elongation of 12 out of 13 tested species were affected by an aqueous solution of juglone (10^{-3} to 10^{-6} M). Growth of eight-week-old seedlings of Japanese larch (*Larix leptolepis*), Norway spruce (*Picia abies*), eastern white pine (*Pinus strobus*) and Scots pine (*Pinus sylvestris*) was also inhibited by

Table 1. Chemical description of juglone

Molecular formula	$C_{10}H_6O_3$
Structural class	Bicyclic napthaquinone. The nearest compound in the same group is plumbagin (2-methoxy-5-hydroxy-1,4-napthaquinone)
Molecular weight	174.16
Description	Yellow needled-shaped crystals from benzene plus petroleum ether
Melting point	161-163°C
Solubility	Slightly soluble in hot water; soluble in methyl and ethyl alcohol, acetone, chloroform, benzene and acetic acid.

Table 2. Plant species reported to be susceptible to the allelopathic effect of juglone.

Parameter	Species	References
Herbs	*Trifolium incarnatum*, *Coronilla varia., Vicia villosa, Lespedeza stipulacea*, and *Lespedeza cuneata, Medicago sativa*, *Lycopersicon esculentum*	(Bode, 1958; Reitveld, 1983)
Shrubs	*Acer ginnala*, *Caragana arborescens*, *Elaeagnus angustifolia*, *Elaeagnus umbellata*, *Lonicera maackii*	(Reitveld, 1983)
Trees	*Quercus alba*, *Fraxinus americana, Liriodendron tulipifera, Alnus glutinosa, Pinus strobus,P.sylvestris, Larix leptolepis, Malus* spp., *Picea abies*	(Funk et al., 1979; Harborne, 1988; Reitveld, 1983)

juglone (Funk et al., 1979). Table 2 describes the allelepathic effect of juglone on different plant species.

Toxicity of juglone against other than plants

Juglone has also been studied extensively for its toxicity against other (non-plant) organisms. The toxicity mechanism of juglone is either by oxidative stress or by electrophilicity (Gant et al., 1986; Öllinger and Brunmark, 1991; Varga et al., 1996). In general, juglone was more cytotoxic than the parent molecule 1, 4-napthoquinone (Doherty et al., 1987; Babich and Stern, 1993). Juglone promoted skin tumors in female Swiss mice pretreated with a sub-carcinogenic dose of dimethyl benzene anthracene (DMBA) followed by dermal application of juglone for a year. However, skin tumors were not observed following the treatment of juglone without pretreatment with DBMA (Van Duuren et al., 1978). The registry of toxic effects of chemical substances (RTECS) describes juglone as an equivocal tumorigenic agent (lungs, thorax and respiration, skin and appendages) on the basis of a 29-week skin painting study in mice (NLM, 2005).

Juglone in cancer research

Though cytotoxic, juglone has shown effective results against both human leukaemia (HL-60) cells and doxorubicin-resistant human leukaemia (HL-60R) cells (Segura-Aguilar et al*.,* 1992). Okada et al. (1967) reported that juglone prevented cancer affected cells from entering mitosis. In juglone-treated tumors, chromosomes in the prophase stage of cell division appeared diffused and sticky, and accumulation of abnormal metaphase figures occurred. Juglone showed antimutagenicities in *Salmonella typhimurium* (Edenharder and Tang, 1997). Sugie et al. (1998) reported that male rats on a juglone-rich diet had a lower incidence and multiplicity of tumors in the small intestine after administration of azoxymethane (a carcinogen particularly effective in inducing colon carcinomas or malignant tumor). They suggested that juglone could be a promising chemopreventive agent for human intestinal neoplasia (growth of an abnormal mass of tissue). Juglone is reported to be a strong inhibitor of the peptidyl-prolyl isomerase Pin1 (Chao et al., 2001). Depletion of Pin1 in various human cancer cell lines resulted in to mitotic arrest in cancer cells and apoptosis or cell death (Zhang et al*.,* 2008), whereas its over-expression was observed in several types of cancers with its possible role to promote tumorigenesis induced by oncogenes such as Ras and Neu, as well as to regulate molecules that facilitate persistent proliferative capacity (Finn and Lu, 2008). Pin1 is a potential therapeutic target for anticancer research and juglone being its inhibitors may be potential anticancer drug. In the treatment of tamoxifen-resistant breast cancer, role of Pin1 was studied as it is an important determinant of resistance to tamoxifen (a drug to treat breast cancer). The results showed that Pin1 increases E2F-4- and Egr-1-driven expression of LC-3; an autophagosome marker is highly expressed in the cytoplasm of cancer cells, but not in noncancerous. Juglone, a potent Pin1 inhibitor, significantly suppressed the TPA-induced expression of E2F-4 as well as Egr-1 transcription factors, which control *LC-3* gene expression (Namgoong et al., 2010).

CONCLUSION

J. regia is being widely cultivated for nut production in the temperate part of the northern Hemisphere. Apparently it is toxic to some plants but not reported dangerous to human despite it has been in human food chain as nuts for long time. Lately interest in juglone increased because of its role in cure of cancer. Juglone's role is evident in preventing the growth of cancerous tissues as well as its inhibition of the peptidyl-prolyl isomerase Pin1 and so it has a therapeutic role in cancer cure. Also efficacy of anti cancer drugs increased when applied along with juglone. Now there is need of more trial of juglone on different type of cancers as well as its application in combination with different types of anti cancer drugs against cancer which certainly will establish role of juglone in cure of cancer.

REFERENCES

Babich H, Stern A (1993). *In vitro* cytotoxicities of 1, 4-napthoquinone and hydroxylated 1, 4- napthoquiones to replicating cells. J. Appl. Toxicol., 13(5): 353-358.

Bode HR (1958). Contributions to the knowledge of allelopathic phenomena in some Juglandaceen. Planta, 51: 440-480.

Cai LW, Bijl G, Vander P, Wu CD (2000). Namibian chewing stick, *Diospyros lycioides*, contains antibacterial compounds against oral pathogens. J. Agric. Food Chem., 48(3): 909-914.

Chao SH, Greenleaf AL, Price DH (2001). Juglone, an inhibitor of the peptidyl-prolyl isomerase Pin1, also directly blocks transcription. Nucleic Acids Res., 29(3): 767-773.

Dama LB (2002). Effect of naturally occurring napthoquinones on root-knot nematode *Meloidogyne javanica.* Ind. Phytopathol., 55(1): 67-69.

Doherty MD, Rodgers A, Cohen GM (1987). Mechanisms of toxicity of 2- and 5-hydroxy-1, 4-napthoquinone; absence of a role for redox cycling in the toxicity of 2-hydroxy-1, 4-napthoquinone to isolated hepatocytes. J. Appl. Toxicol., 7(2): 123-129.

Edenharder R, Tang X (1997). Inhibition of the mutagenicity of 2-nitrofluorene, 3-nitrofluoranthene and 1-nitropyrene by flavonoids, coumarins, quinones and other phenolic compounds. Food Chem. Toxicol., 35(3-4): 357-372.

Erdemoglu N, Küpeli E, Yesilada E (2003). Anti-inflammatory and antinociceptive activity assessment of plants used as remedy in Turkish folk medicine. J. Ethnopharmacol., 89: 123-129.

Finn G, Lu KP (2008). Phosphorylation-specific prolyl isomerase Pin1 as a new diagnostic and therapeutic target for cancer. Curr. Cancer Drug Targets, 8(3): 223-229.

Funk DT, Case PJ, Rietveld WJ, Phares RE (1979). Effects of juglone on the growth of coniferous seedlings. For. Sci., 25(3): 452-454.

Gamble JS (1902). A Manual of Indian Timber. Sampson Low, Martson and Company Ltd. London.

Gant TW, Doherty MD, Odowole D, Sales KD, Cohen GM (1986). Semiquinone anion radicals formed by the reaction of quinones with glutathione or amino acids. FEBS Lett., 201(2): 296-300.

Gîrzu M, Fraisse D, Carnat AP, Carnat A, Lamaison JL (1998). High-performance liquid chromatographic method for the determination of juglone in fresh walnut leaves. J. Chromatogr., 805: 315-318.

Gleeson SK (1982). Heterodichogamy in walnuts: inheritance and stable ratios. Evolution, 36: 892-902.

Harborne JB (1988). Introduction to Ecological Biochemistry. London-New York, Acad. Press.

Hemery GE (2000). Genetic Variation in *Juglans regia.* D.Phil. Thesis. Department of Plant Sciences. Univ. Oxford. Oxford. UK.

Huntley B, Birks HJB (1983). An Atlas of Past and Present Pollen Maps for Europe: 0 - 13000 years ago. Cambridge Univ. Press, Cambridge.

Jackson D, McNeil D (1999). Walnuts. Temperate and Subtropical Fruit Production. 2nd edition (Eds Jackson and Looney), CABI Pub. Oxford.

Jalas J, Suominen J (1976). Atlas Florae Europeae, Vol. 3. The Committee for mapping the Flora of Europe, Helsinki.

Kolov O (1998). Ecological characteristics of the walnut-fruit forests in Kyrgyzstan. In Biodiversity and Sustainable Use of Kyrgyzstan's Walnut-Fruit Forests (eds. J. Blaser, J.Carter and D. Gilmour), IUCN, Gland, Switzerland and Cambridge, UK and INTERCOOPERATION, Bern, Switzerland. pp. 59-62.

Manning WE (1978). The classification within the Juglandaceae. Ann. Miss. Bot. Gard., 65: 1058-1087.

Manos PS, Stone DS (2001). Evolution, phylogeny and systematics of the Juglandaceae. Ann. Miss. Bot. Gard., 88(2): 231-269.

Namgoong GM, Khanal P, Cho HG, Lim SC, Oh YK, Kang BS, Shim JH, Yoo JC, Choi HS, (2010). The Prolyl Isomerase Pin1 Induces LC-3 Expression and Mediates Tamoxifen Resistance in Breast Cancer. J. Biol. Chem., 285(31): 23829-23841.

NLM (2005). Registry of Toxic Effects of Chemical Substances (RTECS), Bethesda, MD, Nat. Lib. Med.

Okada TA, Roberts E, Brodie AF (1967). Mitotic abnormalities produced by juglone in Ehrlich ascities tumor cells. Proc. Soc. Expt. Biol. Med., 126: 583-588.

Öllinger K, Brunmark A (1991). Effect of hydroxy substituent position on 1, 4 -napthoquinone toxicity to rat hepatocytes. J. Biol. Chem., 266(32): 21496-21503.

Polunin O (1977). Trees and Bushes of Britain and Europe. Granada Pub. Ltd, Paladin Frogmore, St Albans Herts. pp. 204.

Reitveld WJ (1983). Allelopathic effects of juglone on germination and growth of several herbaceous and woody species. J. Chem. Ecol., 9(2): 295-308.

Roach FA (1985). Cultivated Fruits of Britain: Their Origin and History. Blackwell Pub., Oxford.

Schneiderhan FJ (1927). The black walnut (*Juglans nigra* L.) as a cause of death of apple trees. Phytopathology, 17: 529-540.

Scisciolo B, De LDJ, Walton DC (1990). Seasonal patterns of juglone in soil beneath *Juglans nigra* (black walnut) and influence of *J. nigra* on understory vegetation. J. Chem. Ecol., 16 (4): 1111-1130.

Segura-Aguilar J, Jönsson K, Tidefelt U, Paul C (1992). The cytotoxic effects of 5-OH-1, 4-napthoquinone and 5,8-diOH-1, 4-napthoquinone on doxorubicin- resistant human leukemia cells (HL-60). Leuk. Res., 16(6-7): 631-637.

Sugie S, Okamoto K, Rahman KMW, Tanaka T, Kawai K, Yamahara J, Mori H (1998). Inhibitory effects of plumbagin and juglone on azoxymethane-induced intestinal carcinogenesis in rats. Cancer Lett., 127(1, 2): 177-183.

Thakur Ajay (2006). Genetic Variation in *Juglans regia.* Ph.D. Thesis. School of Agric. For. Univ. Wales, Bangor, UK.

Thakur A, Cahalan C (2011). Geographical Variation of *Juglans regia* L. in Juglone Content: Rapid Analysis Using micro plate reader. Curr. Sci., 100(10): 1483-1485.

Thomson RH (1957). Naturally Occuring Quinines. Butterworth Scientific Pub., London.

Townsend CC (1980). Juglandaceae. In Flora of Iraq, Vol. 8 (eds C.C. Townsend and E. Guest), Ministry of Agric. Agrar. Reform, Baghdad, pp. 56-61.

Tutin TG, Burges NA, Chater AO, Edmondson JR, Heywood VH, Moore DM (1993). Juglandaceae. In Fl. Europ., (2nd edn.) Vol. 1. (ed. D .M.

Moore). Cambridge Univ. Press, Cambridge.
Van DBL, Segal A, Tseng SS, Rusch GM, Loewengart G, Maté U, Roth D, Smith A, Melchionne S, Seidman I (1978). Structure and tumor promoting activity of analogues of anthralin (1,8-dihydroxy-9-anthrone). J. Med. Chem., 21(1): 26-31.
Varga Z, Bene L, Pieri C, Damjanovich S, Gáspár R (1996). The effect of juglone on the membrane potential and whole-cell K+ currents of human lymphocytes. Biochem. Biophy. Res. Comm., 218(3): 828-832.
Westfall BA, Russell RL, Auyong TK (1961). Depressant agent from walnut hulls. Science, 134: 1617.
Westwood MN (1977). Temperate Zone Pomology. W.H. Freeman and Co., San Francisco.
Zhang CJ, Zhang ZH, Xu BL, Wang YL (2008). Recent advances in the study of pin1 and its inhibitors. Acta, Pharm. Sin., 43(1): 9-17.
Zohary D (1993). Domestication of Plants In Old World: The Origin and Spread of Cultivated Plants In West Asia, Europe And Nile Valley. Oxford Univ. Press, Oxford.