Toxicity/Safety on Cissus Quadrangularis (Bonton Capsule)

TOXICITY/SAFETY

Acute oral toxicity study of *Cissus extract* in Sprague Dawley rats was performed in compliance with the OECD Guidelines for testing of Chemicals, Section 4, and No.420-Acute oral Toxicity –Fixed Dose Method, adopted 17 December 2001.*Cissus extract* did not cause any mortality in female rats treated at 2000mg/kg following dosing and during the observation period of 14 days post dosing. No abnormal clinical signs were observed in treated rats throughout the observation period. It did not induce any adverse effects on the body weight gain of rats treated at 2000mg/kg. No gross pathological alterations were detected in the treated at terminal necropsy. Thus LD50 of Cissus extract was found to be more than 2000mg/kg. No Phytochemical test report was provided for the sample provided.

PHARMACOLOGY

Bone Fracture healing

Cissus quadrangularis is found to contain vitamins and steroids which are found to have specific effect on bone fracture healing. The anabolic steroidal principles from Cissus quadrangularis showed a marked influence in the rate of fracture- healing by influencing early regeneration of all connective tissues involved in the healing and quicker mineralization of the callus.

Study 1: -

Systemic use of Cissus quadrangularis in rats caused complete restoration of normal composition of bone after fracture in 4 weeks while the controls required six weeks. Thus there was a shortening of about two weeks in the bone healing duration. The total weight of the fractured bone also came down towards normal much earlier than the controls indicating quickest bone remodeling. The dogs' examination of the specimen of fractured bone revealed at a less tissue reaction around the fractured area of the treatment animals

than that of the controls. All the sequence of events namely fibroblastic phase (first week) collagen phase (second week) and osteochondroital phase (third and fourth weeks) were hastened by about 10 to 14 days in the treated group. This hastening in the fracture healing is attributed to the stimulation of all the cells of mesenchyma origin, namely the fibroblasts, the chondroblasts and osteoblasts by Cissus quadrangularis. It has greater impact on osteoblastic proliferation than other cellular responses. In both the models the mucopolysaccharide and collagen levels of the bones in the treated group came down to normal at the end of only four weeks while the controls required 6 weeks, as confirmed with histological and histochemical observations.

Ref: K N Udupa and Guru Charan Prasad Further studies on the effect of Cissus quadrangularis in accelerating fracture healing. Ind. Jour. Med. Res. 52,1, January, 1964

Study 2: -

Radioactive calcium (Ca^{45}) studies indicated that Cissus quadrangularis causes less lowering of Ca^{45} uptake in the treated animals while in the control animals there was a greater decrease in the Ca^{45} uptake in the first week followed by a gradual increase in the subsequent weeks which reached its maximum in the 4^{th} week. The Ca^{45} uptake in the treated group came to normal at the end of 5^{th} week as compared to 6-8 weeks in controls. Thus it is concluded that Cissus quadrangularis causes less amount of tissue reaction in the fractured region leading to optimum decalcification in the early stage with minimum of callus formation. Hence deposition of calcium is just enough to join the two broken segments of bone so that it's remodeling takes much faster in the treated group as compared with controls. This early completion of calcification process and earlier remodeling phenomenon lead to early recovery of animals. The tensile strength studies indicated much early gain in the tensile strength in Cissus quadrangularis treated group leading to 90 per cent of gain of its normal strength at the end of 6 week in comparison to 60 per sent of gain in strength in the controls. Thus

Cissus quadrangularis builds up the chemical composition of the fractured bone namely its mucopolysaccharides, collagen, calcium, phosphorus and others as well as its functional efficiency.

Ref: K N Udupa, and Gurucharan Prasad Biomechanical and calcium 45 studies on the effect of Cissus quadrangularis in fracture repair Ind.Jour.Med.Res, 52,5 May 1964.

Study 3: -

Healing of the fractured bone is delayed considerably by the administration of cortisone. The periosteal reaction is reduced and the amount and density of callus is lowered. The mortality rate of the treated subjects is very high due to severe body wasting, atrophy of muscles and gastric perforation. Cissus quadrangularis treatment in these cortisone treated rabbits caused a significant increase in mucopolysaccharides level and also caused proliferation of osteoblastic, chondroblastic and cartilage proliferation. It also led to increased mineralization in the callus. Thus the parenteral administration of the total extract of Cissus quadrangularis not only neutralizes the anti-anabolic effect of cortisone in healing of fractures but also enhances the mineralization of the callus. This effect was much greater than that of anabolic hormone durabolin a drug of choice for the neutralization of cortisone possibly due to its vitamin contents.[26]

Ref: K N Udupa, and Gurucharan Effect of Cissus Quadrangularis The Healing of Cortisone Treated Fracture Ind.Jour.Med.Res, 51,4, July 1963

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Study 4: -

A clinical study was planned to evaluate the effect of the Cissus quadrangularis in the healing of fractures. All of the sixteen patients recruited with various types of fractures were treated with external application of the paste prepared from the herb Cissus quadrangularis. This treatment was given in addition to the standard treatment of fractures, e.g. complete immobilization. As per radiological observations the results were excellent in 6 cases with the 40% reduction in the healing time, good in 8 cases with 53% reduction in the healing time and poor in 1 case with 7% reduction in healing time. Clinically in about 80% of the cases excellent results were observed and in the remaining 14% of the cases the results were good. Only in one case there was no demonstrable effect. In few of the treated cases although radiologically only an early callus formation was observed but clinically the symptoms of fracture such as pain, tenderness, and swelling were significantly absent. These cases could use their limb without fear of pain owing to the confidence they have gained from the absence of clinical symptoms. It was also observed that the injured bones surrounded by muscles showed a greater beneficial effect of this herb than those that are subcutaneous. It was hypothesized that Cissus quadrangularis helps in the earlier formation of collagen fibres leading to earlier calcification and callus formation.27

Ref: K N Udupa Cissus quadrangularis in healing of fractures A clinical study J. Indian medical association, Vol 38, No 11, June 1, 1962

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Study 5: -

A trial was undertaken to evaluate the effect of Cissus quadrangularis extract on the healing process of experimentally fractured radius-ulna of dog. Histopathological and radiological investigations on 11th day revealed faster initiation of the healing process and a greater decrease in serum calcium level in the treated group than the control group. On 11th day treated group exhibited initiation of osteogenesis which was absent in the control group. Fracture was completely healed in 21 days in the treated group and remained incomplete in the control group. Radiograph of the treated group revealed almost complete bridging of the fractured ends with extensive bony deposition and peristoneal reaction compared to that of control group. The treated group also revealed replacement of cartilaginous cells by osteoblastic cells and union of the fractured gap at several places with the formation of new bony trabeculae whereas bony trabeculae were absent in the control group.[20]

Ref: D.K. Deka, L.C Lahon, Effect of Cissus Quadrangularis in accelerating healing process of experimentally fractured Radius- Ulna of Dog, A preliminary study. Indian Journal of Pharmacology 1994 , 26, 44-45

Alkaline phosphates are involved in bone formation and healing of fractures. The enzyme, secreted by the osteoblasts accelerates the process of mineralization either by increasing the local concentration of inorganic phosphate or activating the collagen fibres to induce deposition of calcium salts. Cissus quadrangularis has caused an increase in alkaline phosphates levels during fracture healing in adult dogs. However the difference in mean values for its increase was not statistically significant. [9]

Ref: S S Chopra, M R Patel, L P Gupta and I C Datta, Studies on Cissus quadrangularis in Experimental Fracture Repair: Effect on Chemical Parameters in Blood, Ind.J Med.Res 63,6 June 1975

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Study 6: -

A study was conducted using albino rats to explore whether the beneficial effect of Cissus quadrangularis in the healing of fractures is due to its vitamin C content. The animals receiving Cissus quadrangularis showed rapid accumulation of larger quantity of mucopolysaccharides in the first week followed by more rapid fall and its earlier disappearance from the fractured area and both of these actions have beneficial effect on the healing of the fractures. . At the end of the third week the skiagram showed greater amount of calcification in the Cissus quadrangularis treated group in which one could hardly see a gap at the site of the fracture, while the control and vitamin C treated group showed some gap. At the end of 5^{th} week the union at the fractured site was more firm in the Cissus quadrangularis treated group than the others. Earlier disappearance of mucopolysaccharides from the fractured area is associated with the earlier calcification and firmer callus formation. Mucopolysaccharides play an important role in the healing by supplying raw materials for repairs. Therefore it seems that in the early period the greater the accumulation of these materials more rapid will be the rate of healing. In the latter period where the mucopolysaccharides content decline in the fractured area is an indicative of rapid utilization of these raw materials leading to earlier completion of healing process. This effect of the Cissus quadrangularis drug is not due to its vitamin C content alone, since the administration of the vitamin C to normal animals did not produce such a beneficial effect. Presumably its action in more systemic, which might be responsible for the greater mobilization of mucopolysaccharides from the tissues in to the blood and earlier utilization of the substances required in the healing process.[21]

Ref: K N Udupa.* H J Arnikart, L M Singh, Experimental Studies of the use of Cissus Quadrangularis in Healing of Fracture, The Indian Journal of medical sciences, P-551

Study 7: -

Phosphorus 32 is a useful isotope to study the rate of mineralization during healing of fractures since it is readily incorporated in the area where the calcium phosphate complex is deposited during the latter part of healing. In control animals, such a mineralization process takes place at the site of fracture during the latter half of the third week. This is accompanied with the fall of mucopolysccharides in the region. In animals treated with Cissus quadrangularis such a mineralization process takes place much earlier, roughly in the second half of the second week. Not only the healing has been faster but also the quality of the callus seems to be better in terms of the enormous deposition of the minerals at the end of the second week only. This is followed by early demineralization so that the callus becomes remodeled to take a normal shape of the bone. These findings further confirm our earlier report that the herb Cissus quadrangularis has favorable action in the rate of healing of fracture in experimental animals.[19]

Ref.: L. M Singh and K N Udupa, Studies on Cissus Quadrangularis in Fracture by using Phosphorus – Part II, The Indian Journal of Medical Sciences, p- 926

Study 8: -

Analgesia

Cissus quadrangularis exhibited significant analgesic activity compared to that of Aspirin when tested using Haffner's clip and Eddy's hot plate methods. The optimal effective dose for analgesic effect lay between $1/20^{th}$ to $1/10^{th}$ of its LD_{50}, which indicates its wide margin of safety for the treatment of pain. This analgesic effect of Cissus quadrangularis may be of great value in relief of pain associated with bone fractures.[23]

Ref: ***S.P. Singh N. Mishra , An experimentally Study of Analgesic activity of Cissus quadranguaris Ind. J. Pharmac (7984), 162***

Antibacterial

Alcoholic extract of the stem showed activity against Escherichia coli. [14]

Ref: ***Wlth India -- Raw Materials, II, 184; Fl Br Ind, I, 645;***