HOMOEOPATHIC PATHOGENESES OF CARDUUS MARIANUS AND TNF-α MEDIATED ACTIVITY OF SILYMARIN/SILIBININ

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Abstract:
Background - *Carduus marianus* is commonly known as Milk thistle. In herbal medication it is used in different hepatic disorders. It acts as an antioxidant and free radical scavenger for hepatic protection. The Homoeopathic Materia Medica shows its primary area of action related to hepatic affections. Numerous studies suggest for its beneficial effects on such areas. Beyond that, control of blood glucose level, antineoplastic effects against various carcinoma cells are also found in these studies. Object – to find out the possible background pathophysiologic activities related to these pathogeneses and to corelate with the original pathological changes related to such disorders. Method and Result – numerous clinical or laboratory researches in different animal or human models reveal the common area of TNF-α regulated NF-kB activity is possibly responsible for these affections found in homoeopathic pathogeneses. Conclusion - TNF-α regulated NF-kB activities are thought to be the possible common area of background patho-physiology.

Keywords:
Carduus marianus, Homoeopathic pathogeneses, Silymarin/Silibinin, TNF-α

Introduction:

Carduus marianus, known as Cardus Marianum has been used since the time of ancient physician and herbalists. Its scientific name is Silybum marianum (L.). The word "marianum" comes from the legend that the white veins running through the plant's leave, which were caused by drops of the virgin Mary's milk. When leaving Egypt and looking for a place to nurse the infant Jesus, mother Mary could only find shelter in a bower made by thorny leaves of the Cardus marianum. Dioscorides named it 'Sillybon', Pliny the Elder called it 'Sillybum' and Theophrastus called it 'Pternix'. Dioscoride used it by preparing tea for those that be bitten of serpent. Nicholas Culpepper an English herbalist used it in the treatment of jaundice and for protecting from destruction of liver and spleen. Native Americans used it for the treatment of varicose veins, menstrual difficulties and congestion of liver, spleen and kidneys. [1]

The homoeopathic action of this is centered in the liver and liver related different pathological conditions; with affections of portal system; with abuse of alcoholic beverages; dropsy due to hepatic disease and pelvic congestion; haemorrhage connected with hepatic disease – haemorrhagic piles; influenza when liver is affected; vascular system related to varicosity and ulceration; disorders of respiratory system – asthmatic respiration; disease of miners - associated with asthma; related to sugar metabolism; profuse diarrhoea due to rectal cancer, etc.

Silidianin, Silcristin and Silybin are the three components of this herb. Silybin also called Silymarin or Silibinin is the most active ingredient among them. The action of Silymarin/Silibinin is considered to be as an antioxidant and a free radical scavenger and has hepatoprotective properties. Numerous studies also suggest for its beneficial effects on glycemic indices (such as fasting blood sugar, haemoglobin A1C), antineoplastic effects against various carcinoma cells, like skin, breast, lung, pancreas, colorectal, cervical, prostate, bladder and kidneys. In this regard, its growth inhibiting action by anti-angiogenic mechanisms, which is mediated by decreased tumour associated macrophages and cytokines, especially Tumour Necrosis Factor alpha (TNF-α). [2,3]

Activity of TNF-α:

TNF-α is a cytokine that has pleotropic effects on various cell types and major regulator of inflammatory responses. It activates nuclear factor kappa B (NF-kB, a protein complex that controls transcription of DNA) and mitogen-activated protein kinases (MAPK, the

Serine/Threonine-specific protein kinase that converts extracellular stimuli into a wide range of cellular responses), which results inflammation and cell survival. On the other way, it is also responsible for activation of Mixed lineage kinase domain-like (MLKL, the terminal protein in the pro-inflammatory necroptotic cell death program) and induces macroptosis and inflammation. TNF-α is a crucial component for a normal immune response and activate the immune system to regulate. But the inappropriate or excessive production of it is very dangerous.[4]

Action related to homoeopathic pathogeneses of *Carduus marianus* –

1. Liver affection: Higher serum TNF-α levels in subjects without nonalcoholic fatty liver disease (NAFLD) were associated with the development of NAFLD. The results of study might suggest a pathologic role of inflammation in NAFLD.[5]
2. Portal system affections: TNF-α driven inflammatory processes are important in the development of portal hypertension and the hyperdynamic state.[6]
   TNF-alpha triggers Hepato-pulmonary syndrome in prehepatic portal hypertension.[7]
3. Vascular system affection: TNF-α activates Matrix Metalloproteinases-9 (MMP-9) gene expression and mediates vascular smooth muscles migration and neointimal formation. Increase in venous pressure/wall stretch increases MMP-2 and MMP-9 expression, which in turn produces venous dilation and further increases in venous pressure, leading to a recalcitrant cycle and progressive venous dilation. And this process is considered as potential implications in varicose veins. [8,9]
4. Influenza: Influenza A virus belongs to a group of viruses that induce TNF-α production. Influenza A virus infections are commonly associated with symptoms that suggest involvement of TNF-α. [10]
5. Insulin resistance related to sugar metabolism: Increased TNF-α production has been observed in adipose tissue derived from obese rodents or human subjects and TNF-α has been implicated as a causative factor in obesity-associated insulin resistance and the pathogenesis of type 2 diabetes. [11]
6. Cancer – Colorectal cancer: There is a link between inflammation and cancer, and TNF-α plays a significant role in this process. It acts not only as a pro-inflammatory cytokine, but can also cause tumor development. TNF-α serves as an important indicator of disease progression of Colorectal cancer. [12]
7. Respiratory system affections – Coal Workers' Pneumoconiosis: Involvement of Matrix metalloproteinases (MMP), especially MMP-2 and MMP-9, in acute lung injury and acute respiratory distress syndrome. TNF-α is implicated in asthma, chronic bronchitis, COPD, acute lung disease and ARDS. [13,14]
   TNF-α are found to be associated with the progression of Coal Workers' Pneumoconiosis [15]
8. Alcoholic intoxication and activity of TNF-α: Ethanol administration enhances gut permeability to endotoxin, which acts on Kupffer cells to release TNF-α. It has been found that, TNF-α were increased 2-fold in alcohol intoxicated obese mice. Ethanol intoxication increases TNF-α, but also decreases nuclear NF-κB activity, thus unleashing the apoptotic effects of TNF-α is observed. [16]

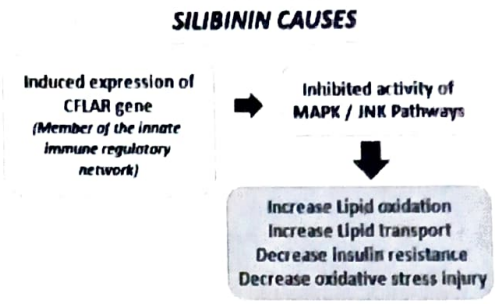
Action of Silymarin/Silibinin:

Silymarin involves suppression of NF-kB by blocking TNF induced activity, a nuclear transcription factor, which regulates the expression of various genes involved in inflammation, cytoprotection, and

carcinogenesis. It also inhibits the TNF induced activation of mitogen activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK, the protein which is a subfamily of MAPK) and abrogated TNF-induced cytotoxicity and caspase activation. In a study it has been found that, silibinin exerts antioxidant and anti-inflammatory properties on human monocytes through an inhibitory effect on H(2)O(2) release and on TNF-α production [17,18]. Silibinin has been found to inhibit MMP-9 gene transcriptional activity. [19]

Action related to homoeopathic pathogeneses of *Carduus marianus* –

1. On TNF-α level: Silibinin has been found to inhibit elevated level of TNF-α significantly. [20]
2. Vascular system: Silibinin inhibits TNF-α-induced endothelin-1 (ET-1) and plasminogen activator inhibitor-1 (PAI-1) expression in endothelial cells. [21]
3. Blood glucose and lipid metabolism: silibinin supplementation can decrease fasting blood sugar (FBS), hemoglobin A1C (HbA1C), and low-density lipoprotein cholesterol (LDL-C), but it has no effect on total cholesterol (TC) or total triglyceride (TG). [3]
4. Non-alcoholic fatty liver disease (NAFLD) - Non-alcoholic steatohepatitis (NASH) is a form of non-alcoholic fatty liver disease which have inflammation with fat and damage in liver. It is a chronic metabolic syndrome. Silibinin can induce expression of Caspase 8 and FADD (Fas-associated death domain)-Like Apoptosis Regulator (CFLAR) gene. And through CFLAR-JNK Pathway it can reverse the process of NASH. For this, on one hand promoting efflux of fatty acids in liver to relieve lipid accumulation, and on the other hand it relieves oxidative stress. [22]



Conclusion:

The drug pathogeneses revealed from different sources like, proving or clinical observations depend on individual's peculiar characters related to its constitution. Group of manifestations may differ from one to another, but the totality of which defines the whole and there must be a certain clue to string these effects together to form a definite pathological state. This pathological state or specific patho-physiological unity is based on characteristic association of different manifestations (expressed or yet to be expressed) originated from specific patho-physiological background. In this respect, the advancement of today's pathological knowledge can provide illuminated patho-physiological background to make more definite identified picture of a drug as well as to find it out in the patient. In this study, the TNF-α regulated NF-kB activity is not only found the one of the important sources of patho-physiological background of the homoeopathic pathogeneses of Carduus marianus, but also provide the unknown areas to be confirmed by proper scientific clinical research in future.