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D-Pinitol - A Natural Phytomolecule and its Pharmacological effect

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Abstract

D-pinitol is a natural compound related to the important family of inositol. It can be found and isolated from many plants, being the active component of ayurvedic remedies from Pinaceae, Asteraceae, Caryophyllaceae, Zygophyllaceous, Cupressaceae, Aristolochiaceae and Sapindaceae. It firstly synthesised and structure characterized from the Sugar pine tree]. D-pinitol is the D-enantiomer of pinitol, it's a 3-O-methyl-D-chiro-inositol. Fortunately, the pharmacological interest in this compound has risen various established multifunctional properties through a variety of signalling pathways: i) anti-cancer, through inhibition of TNF-α and suppression of NF-kB pathway; ii) insulinomimetic and metabolic regulator in type 2 diabetes mellitus, via a post-receptor pathway of insulin action; iii) antioxidant; iv) hepatoprotective; v) immuno-modulator, balancing Th1/Th2 cytokines; vi) osteoporosis preventive, through p38/JNK and NF-kB pathways; vii) anti-aging, via reduction of the insulin/IGF-1 signalling (IIS) pathway; viii) improver of creatine retention; ix) preventive and ameliorative of Alzheimer's disease through selective γ-secretase modulation. Thus, the present review compresses the literature reported to date in relation to the Pharmacological effects and metabolic pathways of this naturally occurring compound D- Pinitol ingredient providing an extensive guide for a future utilization of all of its potentialities. The result came out from the compilation of data brings up with the conclusion i.e. the d-pinitol is the immerging phytomolecule which possess various pharmacological activity and therapeutic potency toward various diseases which makes this molecule as a choice of drug in future for the control of various enlisted disease.

Keywords: d-pinitol, inositol, cyclitols, anti-cancer, anti-diabetic, antioxidant, osteoporosis

Introduction

D-pinitol is pharmacologically active compound occur naturally generally belongs to the important family of inositol, they are generally cyclitol a cyclic polyol, Pinitol is a (3-O-methyl-D-chiro-inositol) [1,2]. Its name comes from "pine" since it was isolated and identified from the heartwood of Pinus monticola for the first time. It is naturally existing compound which was found & isolated from various plants, and it was firstly identified in "Sugar pine" [3]. It can also isolate from synthetic and semi-synthetic method by the mean of various process such as chemical and biochemical transformations [4,5]. D-Pinitol possess many therapeutic properties such as - 1) Ant diabetic; 2) Anti-inflammatory activity; 3) Antioxidant 4) Hepatoprotective; 5) Immuno-modulator; 6) Anticancer; vii) Anti-osteoporosis.

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Structure and properties

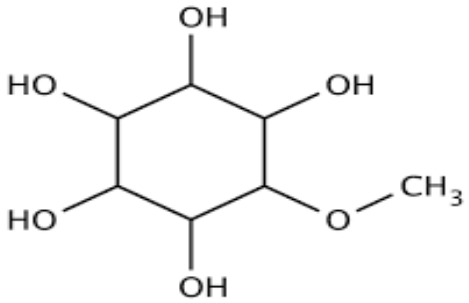
D-pinitol is a compound generally occurs in nature. It firstly synthesised and structure characterized from the Sugar pine tree [6]. D-pinitol is the D-enantiomer of pinitol, it's a 3-O-methyl-D-chiro-inositol [7].

Table 1.Properties of drug

S.No.	Properties	Description
1.	Chemical Name	3-O-methyl-D-chiro-inositol [7]
2.	IUPAC Name	(1S,2S,4S,5R)-6-methoxycyclohexane-1,2,3,4,5-pentol [8-12].
3.	Molecular Formula	$C_7H_{14}O_6$
4.	Molecular Weight	194.18g/mol

Chemical Properties

Table 2.Chemical Properties



S.No.	Properties	Description
1.	Colour	white to off-white [13]
2.	Solubility	water and slightly soluble in ethanol [14]
3.	Melting Point	186–187 ºC [13]
4.	Boiling Point	317.2+ 42.0 ^{0}C at760mmhg [14]

Sources

Natural

D-pinitol and cyclitols can be commonly found in most plants as a group [15,16,17], Due to the side effects of several allopathic drugs and the increase of resistance to currently used drugs canalized people to use plant materials in the treatment of several diseases. It is reported that more than 80,000 plants have exhibited medicinal property among 250,000 plant species, all over the World [18]. However, members of the Leguminosae family are the major natural source of this compound [14,16,19,20,21,22] And the pinitol was found from many other families Pinaceae, Asteraceae, Caryophyllaceae, Zygophyllaceous, Cupressaceae, Aristolochiaceae and Sapindaceae [14,22]

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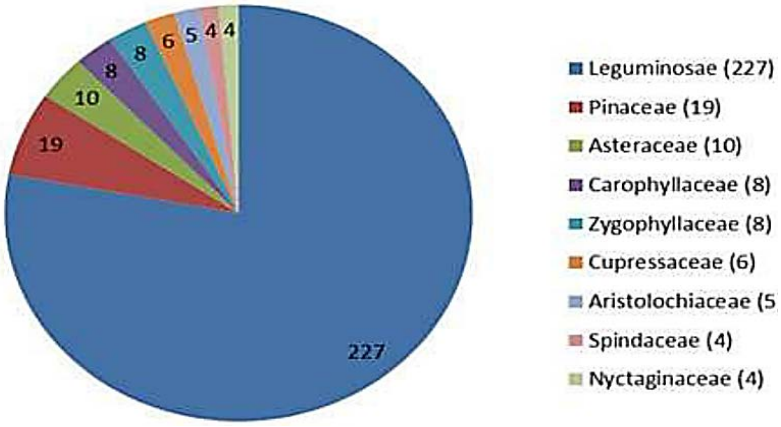


Fig. 1: Distribution of d-Pinitol among various families

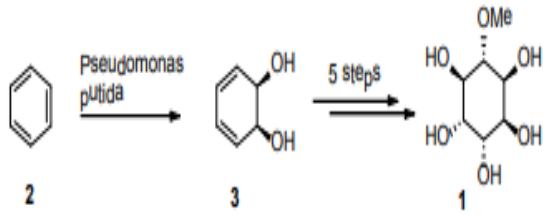
Table 3:Various source of d-pinitol

Plant Name	Family	Part	Reference
Acer oblongum	Aceraceae	Leaves	23
Aristolochia macrophylla	Aristolochiaceae	leaves	24
Aristolochia gigantean	Aristolochiaceae	leaves	25
Aristolochiaarcuata.	Aristolochiaceae	leaves	26
Aristolochiacontorta	Aristolochiaceae	Fruits	27
Artemisia dracunculus	Asteraceae	Fruits	28
Artemisia giraldii	Asteraceae	Aerial parts	29
Artemisia vulgaris L.	Asteraceae	Aerial parts	30
Cardiospermumhalicacabum, Linn	Sapindaceae	leaves	31
Cordia boisieri	Boraginaceae	fruit	32
Cryptomeria japonica D.Don	Cupressaceae	Heart wood, Sap wood	33
Dianthus barbatus cv.	Caryophyllacaea	Aerial parts	34
Dianthus caryophyllus	Caryophyllacaea	Leaves	35
Fagoniaindica	Fagoniaindica	Aerial parts	36
Ginkgo biloba L.	Ginkgoaceae	Grains	37
Gnaphalium pellitum	Asteraceae	Flowers	38
Gnaphalium pellitum	Asteraceae	Flowers	39
Honckenyapeploides (L.)	Caryophyllaceae	Aerial parts	40
Horse chestnut (Aesculus hippocastanum)	Sapindaceae	pericarp	41

Limonium gmelini	Limonium gmelini	leaves and root	41
Lychnis coronaria L	Caryophyllaceae	Leaves	43
mangrove fernAcrostichumspeciosum	Ceratopteridaceae Rhizophoraceae	Leaves	44
Petiveriaalliacea L	Phytolaccaceae	Fruit	45
Phyllocladustrichomanoides	Podocarpaceae	Heart wood	46
Pterodenapparicioi	Leguminosae Wood	Wood	47
Rhamnellagilgitica	Rhamnaceae	Hard wood	48
Rhizophora apiculata Bl	Rhizopharaceae	Roots	49
Sarcophytesanguinea.	Sarcophytaceae	Different parts	50
Sequoia gigantea.	Cupressaceae	Heart wood	51
Sequoia sempervirens.	Cupressaceae	Heart wood	52
Tribulus cistoides	Zygophyllaceae	Aerial parts	53
Tribulus cistoides	Zygophyllaceae	Root	54
Tribulus macropterusBoiss.	Santaraceae	whole parts	55
Zanha Africana	Sapindaceae	Root bark	56
Zanha Africana	Sapindaceae	Root bark	57

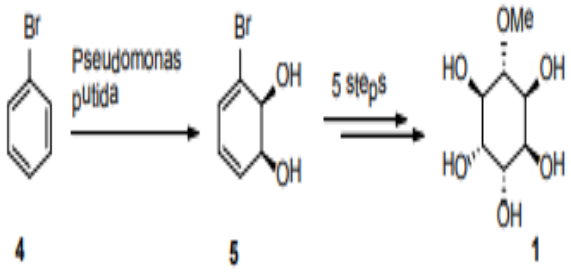
Synthetic

Ley et al. [58] reported the first synthetic method for the preparation of pinitol, who accomplished the preparation of D-pinitol in 35% overall yield starting from benzene (compound 2 in Scheme 1), involving the microbial oxidation of this compound to (1R,2S)-cyclohexa-3,5-diene-1,2-diol (3) followed by 5 synthetic steps (see Ley et al., 1987 for details). Later, these authors improved the strategy to achieve a 49% overall yield [5].



Source 1: Synthesis of D-pinitol (1) from benzene (2)

Hudlicky et al. [4,59] reported a similar methodology starting from microbial oxidation of bromobenzene (compound 4 in Scheme 2) to (1S,2S)-3-bromocyclohexa-3,5-diene-1,2-diol (5). Later on, Aceña et al. [60] reported the throughout synthesis of D-pinitol initating from chiral accessible building blocks in seven synthetic steps with a 10% yield.



Source 2: Synthesis of D-pinitol (1) from bromobenzene (4)

Mechanism of action of d-pinitol

The translocation of GLUT4 from the endoplasmic reticulum to the plasma membrane of skeletal muscle is a major target of insulin to maintain the glucose homeostasis [61]. Treatment with 1 mM D-pinitol increased glucose uptake in vitro in L6 myotubes, and induced the GLUT4

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translocation to the plasma membrane both in vitro and ex vivo [62].

However, the insulin mimetic effect of D-pinitol was not as prominent as expected according to previous in vivo studies[63]; such differences may be due to the variability between these models and timing of administration of D-pinitol prior to glucose intake.

In fact, more recent studies performed by the same group on a C57BL/6 mice in vivo model demonstrated that the oral administration of 1 g/kg bw (body weight) of D-pinitol 30 min before 1 g/kg bw of glucose increased the membrane translocation of GLUT4 in the skeletal muscle and reduced the plasmatic levels of glucose and insulin [64].

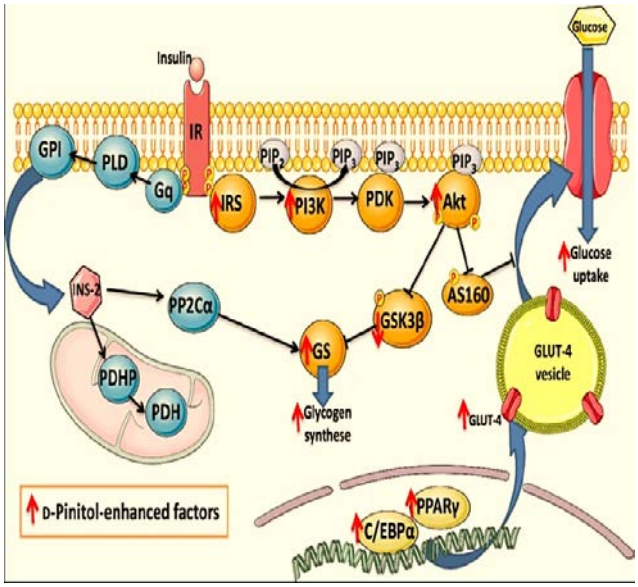

Fig. 2.Suggested mechanism of action of D-pinitol as insulin sensitizer

Source 3.Sanz, M. L.; Martínez-Castro, I.; Moreno-Arribas, M. V. (2008). "Identification of the origin of commercial enological tannins by the analysis of monosaccharides and polyalcohols". Food Chemistry. 111 (3): 778.

Pharmacological Effects of D-pinitol

D-pinitol is reported as a principal compound found in various soy foods and legumes [65,66]. This naturally occurring inositol shows much higher pharmacological potential because of its multifunctional properties (e.g., inositol phosphoglycans generated from lipid and or protein precursors in cell membranes act as insulin-like factors in vitro and in vivo) [65,67-71].

Antidiabetic

Non-insulin dependent (Type 2) Diabetes Mellitus (T2DM) is a chronic disease with associated comorbidities. Nowadays, it is estimated that every year 6.8% of the world's population die due to this illness [72,73]. As a result of the growing on D-pinitol for the treatment of diabetes mellitus and for the pathologies associated to this disease, there are a number of patents protecting these potential exploitations. For example, an international patent was developed by Rademacher Group Ltd.,[74] to defend uses of D-pinitol as an equivalent of inositol phosphoglycans, for different pathologic conditions (e.g., T2DM and obesity). Additionally, specific uses of compositions containing D-pinitol for treating T2DM and related health complications were claimed in USA., by the University of Washington [75] and by the University of Virginia [76], as well as in Korea by Solgent Co. Ltd. [77,78] and by Amicogen Co. Ltd. [79]. Dang et al. [80] demonstrated that the effectiveness of D-pinitol is related to the ability of this compound to stimulate the mobility of Glucose Transporter 4 (GLUT4), which according to its sensitivity to insulin, plays an important role in the regulation of glucose transportation to the skeletal muscle and the adipose tissue. PI3K/Akt signalling pathway is involved in this process through a protein phosphorylation cascade. Therefore, D-pinitol triggers a reduction of plasma glucose levels under certain conditions of high glucose levels. In concordance, Gao et al. [67] pointed out that the amelioration of insulin resistance in T2DM promoted by D-pinitol occurred through the PI3K/Akt pathway, similarly to other inositol phosphates, implicating the PI3Kp85 and PI3Kp110 subunits [81-83]. Thus, the PI3K/Akt pathway that is implicated in a number of human diseases including cancer, diabetes, cardiovascular and neurological diseases [84], is regulated by D-pinitol, resulting in an effective reduction of the concentration of blood glucose through promotion of glycogen synthesis [85].

Anticancer

Breast cancer represents an enormous public health problem nowadays. Thus, for example, it is

the principal cause of mortality and the most frequent cancer in women in the U.S. [86-89]. On the other hand, prostate cancer that is at epidemic proportions, is particularly dangerous because it has a very high tendency to metastasize, particularly to the bone [90-93]. More specifically, it has been demonstrated that prostate cancer expands to distant organs including the liver, bladder, bone, lungs, spine and lymph nodes [94-96]. In this context, the National Cancer Institute (NCI) has highlighted a number of foods for which there are evidences of a reduced risk of suffering cancer if incorporated in the regular diet, including plant-derived foods such as soybean (51a and b). It has been discovered that D-pinitol reduces the progress and attack of certain prostate cancer cells in vitro at non-cytotoxic concentrations [93,94]. Also, D-pinitol has demonstrated preventive efficacy against breast cancer induced in rats [97,98] as well as tumour-growth inhibitory activity through the modulation of the balance between inflammatory cytokines, hormones, tumour markers, lipids and other biochemical processes [99,100], finally resulting in the growth retardation of tumour cells [101].

The mode of action of the D-pinitol to exert its anti-cancer biological activityhas been suggested to be the active blocking of the Nuclear Factor kappa B (NF-kB) pathway, a transcription factor inactively present in the cytoplasm that is activated through its reallocation to the nucleus by an important number of carcinogens and inflammatory agents [101]. In addition, Lin et al. [102,103] found that D-pinitol diminishes in a dose-dependent manner the Focal adhesion kinase (FAK protein) phosphorylation, precisely this is of high interest for treating cancer because FAK is involved in tumour migration and invasion [102,104,105]. Specifically, it has been proven that D-pinitol inhibits cell motility in human prostate cancer cells via the FAK/c-Src signalling pathway [102].

Antioxidant

Oxidative stress has been reported as one of the major causes of tissue damage. Excessive production of free radicals resulting from oxidative stress can damage macromolecules. Increase in malondialdehyde (MDA) is an indicator of oxidative stress [106]. Due to the close relationship that exists between oxidative stress and altered immune functions, increases in the incidence of autoimmune diseases, higher susceptibility to infections, and accentuated prevalence of carcinogenesis phenomena. Sivakumar etal. recently demonstrated the beneficial effect of D-pinitol against oxidative stress [107,108]. The results of the study suggested that D-Pinitol protects the pancreatic tissue from free radical-mediated oxidative stress in addition to its antidiabetic property [107**]**

Hepatoprotective

D-pinitol exerts a protective effect of the hepatic, kidney and pancreatic tissues against oxidative stress [107,108]. Special mention is given here to the hepatoprotective action because of the importance of the liver as a vital organ, with critical functions such as for example the detoxification of the body from hazardous substances. Unfortunately, a number of reactive species, including free radicals, can damage the liver leading to jaundice, cirrhosis or fatty liver, to name a few. Additionally, viral hepatitis is considered a major health problem throughout the world [109]. Zhou et al. [110] Proves that D-pinitol shows a protective effect against human viral hepatitis caused by D-galactosamine (GalN) in rat model. Choi et al [71] evidencedthat inositol improves the liver function by lowering the levels of certain serum aminotransferases, such as aspartate transaminase (AST) and alanine transaminase (ALT).[71]

Immuno-suppressor

A proper function of the immune system is of very important. Immunodeficiency may occur as a result of certain diseases (e.g., HIV/AIDS/CANCER). A hyperactive immune system leads to serious health problems or autoimmune diseases such as rheumatoid arthritis, type 1 diabetes or lupus erythematosus, to name a few. Asthma, chronic inflammatory processes and a propensity for allergic responses are also the manifestation of a hyperactive immune system [111]. Thus, D-pinitol administration in rats showed very good anti-inflammatory activity, demonstrated by means of the adequate models of chronic inflammation, such as the induction with carrageenan and cotton pellets [112], as well as a remarkable inhibitory capacity of asthma [113]. Thus, Lee et al. [113,114] found that D-pinitol reduced the increased levels of the Th2 cytokine

IL-4, a result corroborated by Chauhan et al. [115].

Anti-osteoporosis

Bone is a complex tissue made of different types of cells which are continuously experiencing a range of equilibrated processes of formation and resorption. Osteoporosis results from an imbalance between these processes of bone resorption and bone formation leading to a net bone lost. This imbalance can be originated as a consequence of several conditions such as hormonal disturbances or certain diseases or medications (e.g., corticosteroids or anti-epileptic agents) [68,116].Drugs for treating osteoporosis (e.g., bisphosphonates, calcitonin and oestrogen) act by inhibiting the function of osteoclasts that are responsible for bone resorption [68,117]. Unfortunately, these drugs have limited success on recovering bone mass (maximum 2% per year) [68]. In this concern, Liu et al. [68] showed that D-pinitol is capable to inhibit the formation of osteoclasts induced by RANKL. Specifically, this inositol exerts this effect through the p38/JNK and NF-kB pathways. In conclusion, D-pinitol has potential to be used for treatment and prevention of osteoporosis [118].

Anti-aging

Aging can be viewed as an accumulation of changes over time, accompanied with a functional and reproductive decline that is associated with an increased mortality [119,120]. D-pinitol is one of a few compounds known to be capable to mimic DR. Thus, Hada et al. [120] showed that D-pinitol treatment considerably extended life span of Drosophila melanogaster, reducing oxidative stress and improving health, with evident benefits in locomotion. Worth noting, no reduction in fecundity was observed. These authors pointed out a deactivation of the insulin/IGF-1 signaling (IIS) pathway as the most probable mechanism [121,122]. D-pinitol may reduce the cellular levels of the intracellular messenger phosphatidylinositol (3,4,5)-triphosphate (PIP3), a compound structurally related to D-pinitol that is capable to inhibit dFOXO (single Drosophila melanogaster forkhead box O transcription factor). Then, as dFOXO plays important functions in cell growth, proliferation, differentiation and longevity, D-pinitol facilitates its activation through reduction of its inhibitor PIP3. Hada et al. [120,123] demonstrated that the activation of dFOXO by D-pinitol was acquired by means of the S6K and JNK signalling pathways. Furthermore, a reduction of the inflammatory response, closely related to aging. it was concluded that D-pinitol has great potential to be used as a functional ingredient with anti-aging properties [120]. Consequently, the National Institute of Advanced Industrial Science and Technology (AIST) associated with Tsujiko Co. Ltd., in Japan [124], as well as at Dermalab Co. Ltd., in Korea [125,z26] have protected compositions containing D-pinitol with anti-aging properties.

Meliorative of Alzheimer's disease

Alzheimer's disease is a serious neurodegenerative condition that provokes a progressive deteriorated status of dementia in which synapses are lost [127,128]. nowadays this illness, that affects 13% of people older than 65 in developing countries, is untreatable and fatal [127]. compounds directed to reduce beta Amyloid (Aβ) peptide formation and to facilitate Aβ plaques dissolution are of principal interest, as it is the case for D-pinitol [127,128], a molecule with a high potential for treating this disease [127-137]. D-pinitol has demonstrated improving activity in preclinical models of Alzheimer's disease, making this compound an excellent candidate as a therapeutic agent for this malignancy. D-pinitol, also known as NIC5-15 in clinical trials, is considered a selective γ-secretase modulator (SGSM) that is the general denomination used to identify those molecules that are selectively capable to block the amyloid precursor protein (APP) without interfering with other signalling pathways. Concretely, D-pinitol is alleged to modulate γ-secretase and to reduce Aβ production, although these findings are still in a preliminary stage [127]. Pasinetti in the U.S.A. [135-136] and McLaurin in Europe [137] have patented compositions and uses of D-pinitol for treating Alzheimer's disease.

Conclusion

The pinitol is the natural occurring compound which was isolated from various plants of familyPinaceae, Asteraceae, Caryophyllaceae, Zygophyllaceous, Cupressaceae, Aristolochiaceae and Sapindaceae. Various studies have been performed & the result came out which conclude that the pinitol possess various pharmacological

activities such as anti-diabetic, anti-cancer, hepatoprotective, antioxidant, anti- osteoporosis, anti-aging etc [77]. The studies carried by Goel et al. brings up with the conclusion that d-pinitol should be better substituent for the treatment of diabetes type-2 due to its ability of to stimulate the mobility of Glucose Transporter 4 (GLUT4), which according to its sensitivity to insulin, plays an important role in the regulation of glucose transportation to the skeletal muscle and the adipose tissue[78].

Other studies have been also performed by Hada et al. showed that D-pinitol treatment considerably extended life span of Drosophila melanogaster, reducing oxidative stress and improving health, with evident benefits in locomotion [106].

Pasinetti in the U.S.A. [135-136] and McLaurin in Europe [137] have patented compositions and uses of D-pinitol for treating Alzheimer's disease& reported that D-pinitol has demonstrated improving activity in preclinical models of Alzheimer's disease, making this compound an excellent candidate as a therapeutic agent for this malignancy.

Liu et al. in their research work proven and identified that the D-pinitol is capable to inhibit the formation of osteoclasts induced by RANKL. Specifically, this inositol exerts this effect through the p38/JNK and NF-kB pathways. In conclusion, D-pinitol has potential to be used for treatment and prevention of osteoporosis [118].Lee et al. found that D-pinitol reduced the increased levels of the Th2 cytokine IL-4, a result corroborated by Chauhan et al.and both of them come up with a conclusion that d-pinitol also posse immune suppressant activity[115,119].

National Cancer Institute carried out the set of studies and found that D-pinitol reduces the progress and attack of certain prostate cancer cells in vitro at non-cytotoxic concentrations [93,94]. Also, D-pinitol has demonstrated preventive efficacy against breast cancer induced in rats [97,98] as well as tumour-growth inhibitory activity through the modulation of the balance between inflammatory cytokines, hormones, tumour markers, lipids and other biochemical processes [99,100], finally resulting in the growth retardation of tumour cells [101].The mode of action of the D-pinitol to exert its anti-cancer biological activityhas been suggested to be the active blocking of the Nuclear Factor kappa B (NF-kB) pathway.

The compilation of above literature review enlightens the points that the d-pinitol an active member of family inositol has a potent anti-diabetic & anti-cancer activity which must be a better therapeutic substituent for the treatment of the above mention disease in compare with the existing drugs with lesser side effects.

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