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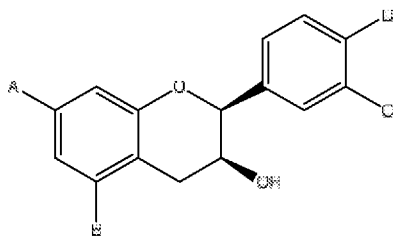
(54) Title: UTILITY OF (+) EPICATECHIN AND THEIR ANALOGS



Formula (I)

(57) Abstract: The present invention pertains to the enhanced activity of (+) epicatechin over (-) epicatechin. The present invention is related to novel analogs of (+) epicatechin of the formula (I), which enhances the pharmacokinetics and therefore the pharmacodynamics of (+) epicatechin. The present invention is related to analogs of (+) epicatechin of the formula (I). The general structure of the analogs of the present invention may be represented by Formula (I): Formula (I) wherein A and B are independently OR1 and C and D are independently OH; wherein R1 is independentlyC1 to C10 lower straight or branched chain acyclic or cyclic alkyl, or is selected from the group comprising, hydroxy butyric acid, dichloroacetic acid; phenyl butyric acid; valproic acid.

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UTILITY OF (+) EPICATECHIN AND THEIR ANALOGS

FIELD OF THE INVENTION

The present invention discloses the utility of (+) epicatechin and analogs of (+) isoform of epicatechin.

BACKGROUND OF INVENTION:

Polyphenolic natural products are important because of their utility in various biological pathways, their occurrence in foodstuffs, and hence their relevance for human health.The stereochemistry of the substituents on a polyphenol monomeric unit of a polyphenol may be described in terms of their relative stereochemistry, "alpha/beta" or "cis/trans". The term "alpha" ( ) indicates that the substituent is oriented below the plane of the flavanol ring, whereas, "beta" ( ) indicates that the substituent is oriented above the plane of the ring. The term "cis" indicates that two substituents are oriented on the same face of the ring, whereas "trans" indicates that two substituents are oriented on opposite faces of the ring.

Catechinspossesstwo benzene rings and a dihydropyran heterocycle (the C-ring) with a hydroxyl group on carbon 3. A ring is similar to a resorcinol moiety while the B ring is similar to a catechol moiety. There are two chiral centers on the molecule, on carbons 2 and 3. Therefore, it has four diastereoisomers. Two of the isomers are in a trans configuration and are called *catechin* and the other two are in a *cis* configuration and are called *epicatechin*.

(+)-Catechin and (-)-epicatechin are the most abundant naturally occurring epimers in cacao. During biosynthesis catechin and epicatechin are predominantly synthesized as (+)-catechin and (-)-epicatechin. However, certain plants such as spotted knapweed (*Centaurea maculosa*, Lam.) demonstrate the presence of racemic catechin and both (+/-)-catechin and (+/-)-epicatechin was described in guaraná seeds (*Paullinia cupana* var. *sorbilis*).

Since, catechin and epicatechin possess two chiral centers; their properties depend on the conformation of the molecules. Since (-)-epicatechin, is the predominantly synthesized or available epimer of epicatechin in cacao or tea, most of the reports of the biological activity tested are for this isomer. The activity of epicatechinsas their individual epimers and/or racemic mixture is not well documented in prior art. The prior art discloses that naturally occurring member of the flavonoid family, (-)-epicatechin as inducing mitochondrial biogenesis in vitro and in vivo, resulting in the successful treatment of diseases associated with mitochondrial depletion, such as muscular dystrophy. Numerous papers and patents discuss the broad use of flavonoids as anti-oxidants or anti-cancer agents. Those teaching this art do not distinguish chiral flavonoids as being uniquely active. Nor has there been any report of stereo selective properties of a unique flavonoid. Rather their effects have typically been described as attributable to all members of the flavonoid class. There are reports in prior art that state that (-) isoform of epicatechin, found naturally occurring in cocoa, green tea, and other plant sources of polyphenols, can prevent acute mitochondrial injury involving the formation of mitochondrial permeability transition pores that damage mitochondrial function by allowing the non-specific diffusion of electrolytes into the mitochondria and that (-)-isoform of epicatechin is capable of inducing mitochondrial biogenesis in *in vivo* models (see WO 2012/170430 and WO 2013/142816). The differences in the activities between the isomers are also not known and documented in the prior art.

Isolation and availabilityof pure polyphenols from natural sources is difficult with increasing degree of oligomerization and has been one of the reasons for the lack of information about the stereochemical difference of activity of the enantiomers of epicatechin and therefore synthesis of polyphenols is preferred. In addition, such polyphenols have certain drawbacks, when used clinically, such as, poor pharmacokinetic profile. Hence there is a need to improve the pharmacokinetic profiles of the polyphenols.

One of the consequences of a means of production of a synthetic epimer is the ability to construct new chemical analogues of a sterochemically defined phenol . The analogues of polyphenols may be used, to improve the pharmacokinetic profile of the polyphenol by, increasing the half-life of the parent drug, which would help decrease the number of doses needed to achieve a desired effect, and/or create a more effective and/or a safer drug.

There are certain prior art drawn to the analogs of epicatchin, WO 2014/162320, the Applicant disclosed certain novel analogs of natural flavonoid phenols, that were biologically active, but the Application, neither discloses the importance of stereoisoforms in activity, nor does the application disclose the mode of activity of these analogs.

Hence, there is a need to examine the utility of the isomers of catechin/epicatechin and also for novel analogs of epicatechin that effectively delivers the preferred isomer.

OBJECT OF THE INVENTION

An object of the invention is to examine the utility of the isomers of epicatechin and also to provide novel analogs of epicatechin that effectively delivers the preferred isomer

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: depicts the activity of (+)-epicatechin in inhibition complex IV on the increase of the expression of Electron Transport Chain IV (ETC IV) in comparison to (-) epicatechin, (+)-epicatechin is approximately 400 fold more potent than (-)-epicatechin-an unprecedented gain of biological potency.

Figure 2: depicts the greater homology to 11-beta-hydroxypregnenolone of (+)-epicatechin compared to that of (-)-epicatechin.

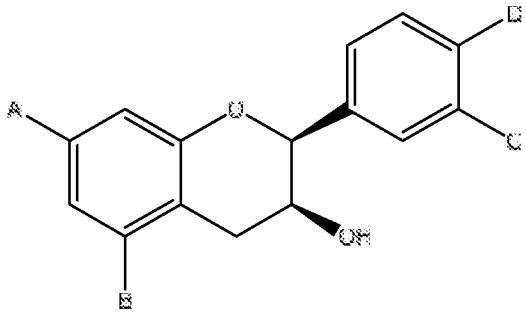
Figure 3: depicts the activity of the compounds on triglycerides content of livers.

BRIEF DESCRIPTION

The present invention pertains to the enhanced activity of (+) epicatechin over (-) epicatechin.

The present invention is related to novel analogs of (+) epicatechin of the formula (I), which enhances the pharmacokinetics and therefore the pharmacodynamics of (+) epicatechin.

The present invention is related to analogs of (+) epicatechin of the formula (I). The general structure of the analogs of the present invention may be represented by Formula (I):



Formula (I)

wherein A and B are independently OR_1 and C and D are independently OH; wherein R^1 is independentlyC_1 to C_{10} lower straight or branched chain acyclic or cyclic alkyl, or is selected from the group comprising, hydroxy butyric acid, dichloroacetic acid; phenyl butyric acid; valproic acid.

The present invention discloses analogs of (+) epicatechin of the formula (I), wherein B is OR_1 and A, C and D are independently OH; wherein R^1 is independently C_1 to C_{10} lower straight or branched chain acyclic or cyclic alkyl,

or is selected from the group comprising, L-Glutamic acid, hydroxy butyric acid, dichloroacetic acid; phenyl butyric acid; valproic acid.

The present invention includes a process for preparation of compounds of the present invention and methods of use comprising the compounds of the present invention.

DETAILED DESCRIPTION

The present invention is based on the unexpected stereo selectivity with respect to the isomers of epicatechin, which has two enantiomers, (-)-epicatechin, and (+)-epicatechin.

A. Activity of (+) Epicatechin compared to (-)Epicatechin

The physical and biochemical properties of stereo isomers can differ significantly and unexpectedly. Enantiomers can differ with respect to activity and physicochemical properties. Stereo selective metabolism of chiral compounds can influence pharmacokinetics, pharmacodynamics, and toxicity. There is no predictability with respect to differential expression of therapeutic or adverse effects among enantiomers (Agranat I et al 2002 Putting chirality to work: the strategy of chiral switches. Nature Reviews Drug Discovery 1:753-768; When one enantiomer has activity of interest, its paired enantiomer typically is either inactive, or an antagonist of the active enantiomer, or has a separate activity that could be undesirable. There is no way to predict or anticipate such outcomes for any given enantiomer (Caldwell, J, 1999, Through the looking glass in chiral development. Modern Drug Discov 2:51-60) .Occasionally both enantiomers may show similar activities to varying degrees. It is more usual to see the greatest degree of variability among the enantiomers of receptor antagonists, as there are many potential ways to sterically obstruct the active site of a receptor. The largest therapeutic variation in potency that we have been able to determine among enantiomers, therefore, are receptor antagonists For example, S (-)-propranol exhibits 100-fold greater receptor antagonism than the R-(+)-propranolol with

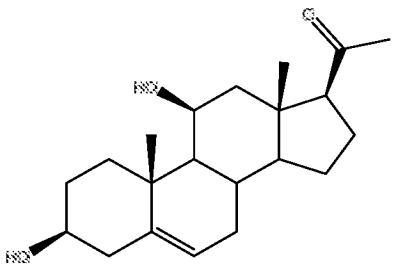
respect to blocking the 1, 2, and 3 adrenergic receptors. (Smith,S, 2009, Chiral toxicology; it's the same only different ToxicolSci 110:4-30). The more restricted requirement of optimal ligand fit to a receptor to activate the receptor normally results in much smaller variation with respect to potency of receptor activation. When paired enantiomers exhibit similar agonist activity, the differences in potency are typical those of a fractional ratio. The prior art does not disclose any examples of differential agonist activity of enantiomers of more than a few fold.

The present invention discloses a remarkable range of biological activity across the two enantiomers of epicatechin, something heretofore not described for flavonoids as a class. The enantiomer of (-)-epicatechin is (+)-epicatechin. When compared in an assay on the increase of the expression of Electron Transport Chain IV (ETC IV), (+)-epicatechin is approximately 400 fold more potent than (-)-epicatechin-an unprecedented gain of biological potency (Figure 1). The data is represented at Table 1:

Table 1: EC_{50} (mM) OF COMPOUNDS ON MITOCHONDRIAL ETC COMPLEXES

Compound	ELCTRON TRANSPORT CHAIN COMPLEX IV
(-)-Epicatechin	0.04
(+)-Epicatechin	0.0001

The basis for the advantageous properties of the (-)- and (+)-isoforms of epicatechin consists of their structural homology to recently discovered hormone that mediates which is set out in the patent application PCT/IN2015/050072:



As shown in Figure 2, (-)-epicatechin possesses two hydroxyl groups that are a steric match for two of the three hydroxyl groups of OHP. However, when (+)-epicatechin is inverted in relationship to (-)-epicatechin and matched against OHP, now all 3 of the hydroxyl groups of OHP display remarkable homology to 3 of the hydroxyl groups of (+)-epicatechin. There is no precedent for the discovery that the inverted 3-dimensional structure of one enantiomer of a compound possesses closer structural and functional homology to a natural ligand when compared to its paired enantiomer.

Therefore, the preferred enantiomer of epicatechin for use is the (+) isoform or the (2S,3S) enantiomer of epicatechin and its analogs, preferably free of contamination with catechin. (+)-Epicatechin results in a superior pharmacological effect when free from other flavonoids, particularly from known isomers of epicatechin.

Without being limited by theory, it is submitted that the compounds of the present invention are active due to their unique configuration and stereochemistry. The compounds of the present invention are useful in treating diseases or disorders that would benefit from modification of Electron transfer Chain (ETC) and particularly electron transfer chain IV.

The present invention provides methods for treating diseases or disorders that would benefit from increased expression of Electron transfer Chain, particularly ETC IV. The methods involve administering to a subject in need thereof a therapeutically effective amount of a (+)-epicatechin.

The vast majority of the body's need for ATP is supplied through the process of oxidative phosphorylation, carried out in the mitochondria in all tissues. There are 5 protein complexes, known as the Electron Transport Complexes that effect ATP synthesis. ETC I, II, III, and IV mediate electron transport. ETC I, III, and IV also

function as proton pumps that maintain an electrochemical gradient necessary for activity of ETC V, the ATP synthase enzyme that makes ATP from ADP. Complex IV, also known as cytochrome c oxidase, (COX), consists of 14 subunits whose assembly into a functional complex requires an additional 30 protein factors. ETC IV is particularly important to oxidative phosphorylation. It is the only one of the ETC complexes to manifest tissue-specific and developmentally regulated isoforms, allowing precise regulation of oxidative phosphorylation under a variety of metabolic demands. Thus the ETC IV (COX) protein complex is considered to be the rate-limiting step in oxidative phosphorylation. Small positive or negative changes in ETC IV can exert a significant impact on health. Selective activation of COX activity has been associated with improved cognition, improved neuronal cell survival under stress, and improved wound healing. Mutations in the numerous proteins that comprise or regulate the activity of ETC IV reveal the pathological consequences of even modest decreases in ETC IV activity. As little as a 30% reduction in COX activity has been shown to induce cardiomyopathy or be associated with the development of neurodegenerative diseases such as Alzheimer's. Decreases in COX (ETCIV) expression due to mutations or molecular manipulation have been associated with loss of muscle endurance and speed, muscle dystonia, immunodeficiency states due to impaired T cell maturation, cardiomyopathy, particularly of the aging phenotype, ataxia, neurodegeneration, increased toxicity in the setting of ischemia, pulmonary inflammation and fibrosis, encephalopathy, vascular insufficiency, and stimulation of cancer cell proliferation. Additional specific diseases associated with COX subunit isoform mutations causing loss of function include exocrine pancreatic insufficiency, inflammatory lung disease, Charcot-Marie-Tooth disease, infantile encephalomyopathy, and Leigh syndrome neurodegeneration with epilepsy.

In summary, the following conditions associated with loss of COX expression or function would be expected to be therapeutically responsive to a potent, preferential inducer of COX (ETC IV) expression: impaired cognition,

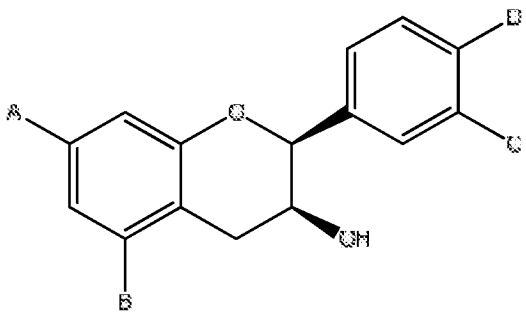
neurodegenerative diseases such as Alzheimer's or Leigh syndrome, dystonia, sarcopenia, cardiomyopathy of aging or other diseases associated with mitochondrial dysfunction, ischemic vascular disease, immunodeficiency states, ataxia, pulmonary inflammation and fibrosis, infantile encephalomyopathy, epilepsy, Charcot-Marie-Tooth disease, exocrine pancreatic insufficiency, impaired wound healing, growth of cancer cells.

In addition, given the relative effect of (+)-epicatechin compared to (-)-epicatechin in lowering the elevated triglycerides of mice on a high fat diet, (+)-epicatechin and its analogs would be the preferred medicament for conditions associated with elevated triglycerides, such as metabolic syndrome, Type II diabetes, congenital hyperlipidemias, and drug-induced hyperlipidemia, as is observed with corticosteroid treatments.

B. Analogs of (+) epicatechin with increased pharmacokinetic property and enhanced utility.

In another aspect, the present application also discloses compounds of formula (I) that are analogs of (+)-epicatechin that possess improved pharmacokinetic properties and enhanced utility.

The general structure of the analogs of the present invention may be represented by Formula (I):



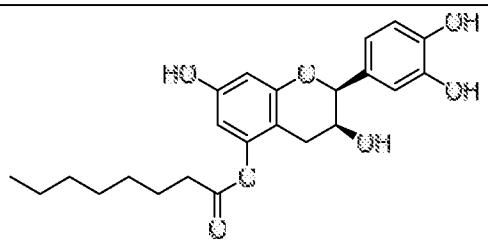
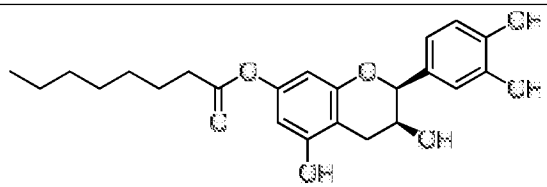
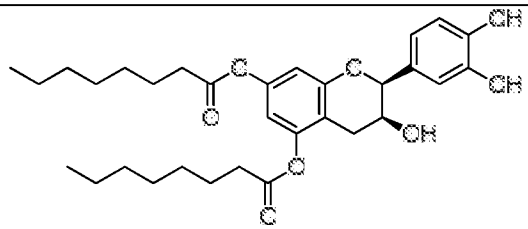
Formula (I)

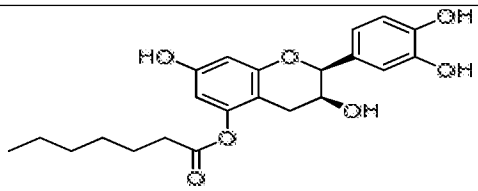
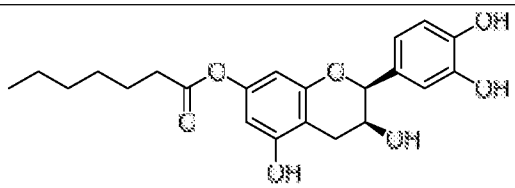
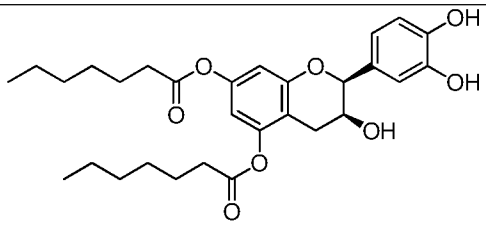
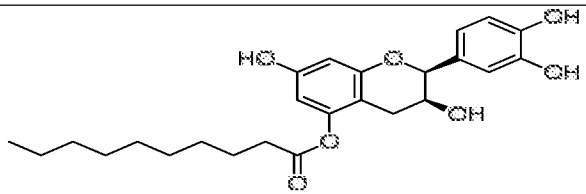
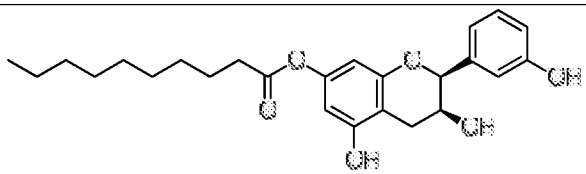
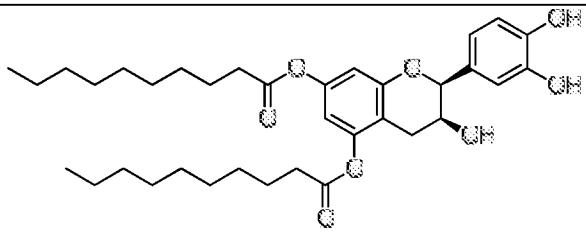
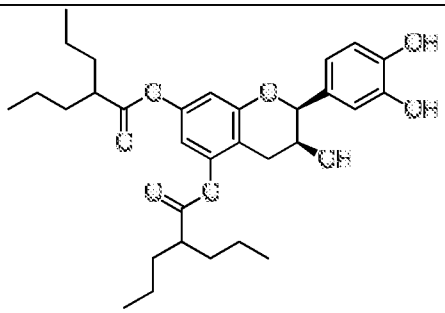
wherein A and B are independently OR_1 and C and D are independently OH; wherein R^1 is independentlyC_1 to C_{10} lower straight or branched chain acyclic or cyclic alkyl, or is selected from the group comprising, hydroxy butyric acid, dichloroacetic acid; phenyl butyric acid; valproic acid.

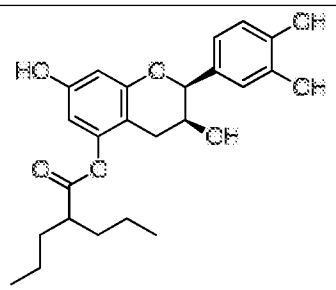
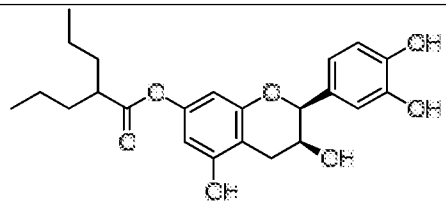
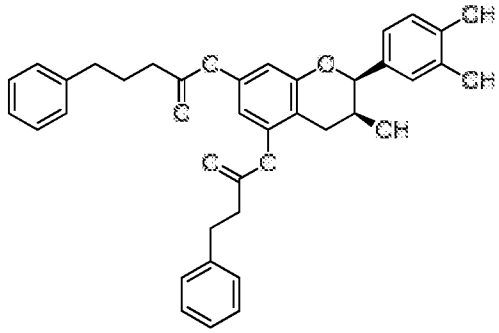
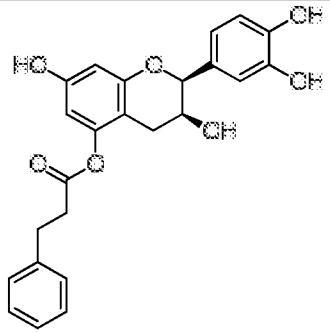
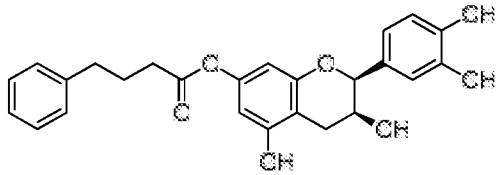
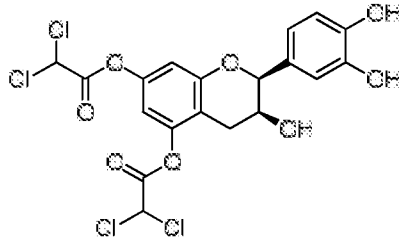
The present invention discloses analogs of (+) epicatechin of the formula (I), wherein B is OR_1 and A, C and D are independently OH; wherein R^1 is independently C_1 to C_{10} lower straight or branched chain acyclic or cyclic alkyl, or is selected from the group comprising, L-Glutamic acid, hydroxy butyric acid, dichloroacetic acid; phenyl butyric acid; valproic acid.

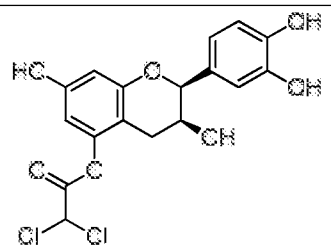
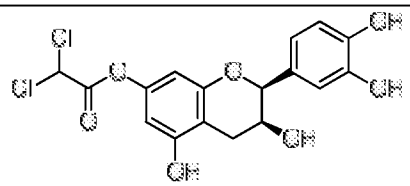
A few illustrative compounds of the present invention are listed at Table 2.

Table 2: Illustrative Compounds of the Present Invention.

S.No.	Structure	IUPAC Name
1001		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl octanoate
1002		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl octanoate
1003		(2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl dioctanoate

1004		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl heptanoate
1005		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl heptanoate
1006		(2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl diheptanoate
1007		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl decanoate
1008		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl decanoate
1009		(2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl bis(decanoate)
1010		(2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl bis(2-propylpentanoate)

1011		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl 2-propylpentanoate
1012		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl 2-propylpentanoate
1013		(2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxy-5-((3-phenylpropanoyl)oxy)chroman-7-yl 4-phenylbutanoate
1014		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl 3-phenylpropanoate
1015		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl 4-phenylbutanoate
1016		(2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl bis(2,2-dichloroacetate)

1017		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl 2,2-dichloroacetate
1018		(2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl 2,2-dichloroacetate

The compounds of the present invention include:

i. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl octanoate;
ii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl octanoate;
iii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl dioctanoate;
iv. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl heptanoate;
v. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl heptanoate;
vi. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl diheptanoate;
vii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl decanoate;
viii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl decanoate;
ix. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl bis(decanoate);
x. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl bis(2-propylpentanoate);
xi. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl 2-propylpentanoate;
xii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl 2-propylpentanoate;
xiii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxy-5-((3-phenylpropanoyl)oxy)chroman-7-yl 4-phenylbutanoate;
xiv. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl 3-phenylpropanoate;

xv. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl 4-phenylbutanoate;

xvi. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl bis(2,2-dichloroacetate);

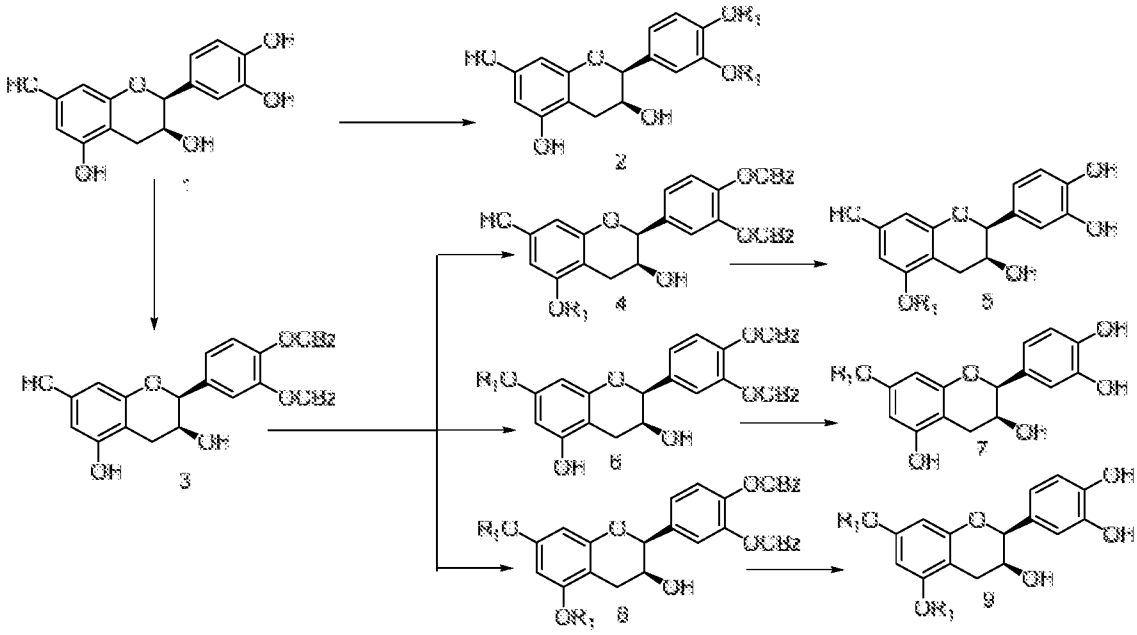
xvii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl 2,2-dichloroacetate;

xviii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl 2,2-dichloroacetate.

C. Synthesis of the compounds of the present invention.

The present invention also relates to a process of preparing the compounds of formula (I).The compounds of present invention may be prepared by the synthetic scheme 1 as here below:

Scheme-1



Some of the compound of present interest can be synthesized from (+)-epicatechin (1) by the scheme outline as above. The (+) isomer of epicatechin can be

synthesized as mentioned in PCT/IN2012/000052, PCT/IN2014/000061, which are incorporated herein in its entirety. The (+) isomer of a polyphenol e.g. epicatechin when treated with a defined quantity of corresponding acylchloride or carbonyl chloride or carbamoylchlorode in presence of base such as DIPEA or TEA or potassium carbonate in a suitable solvent such as acetonitrile or dichloromethane at a temperature range from 0°C to refluxing can provide substituted derivatives of interests represented by compound **2**.

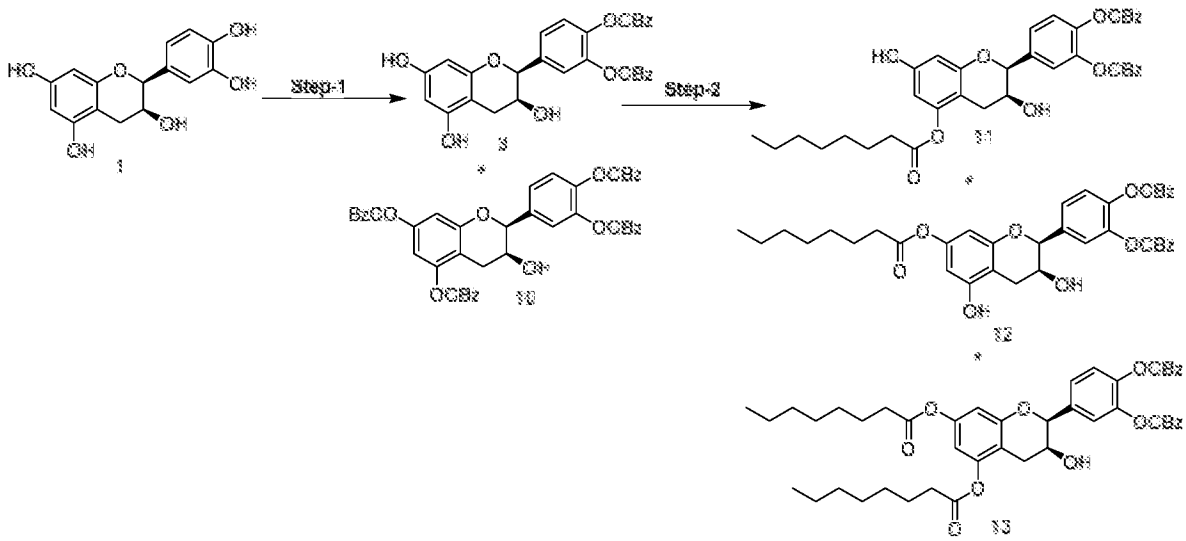
In other case, a (+) polyphenol such as (+)-epicatechin can be protected using a protecting group known in literature such as CBZ-Cl in presence of a base such as TEA in a solvent such as acetonitrile at temperature ranging from 0°C to refluxing to give the compound represented by **3**. Compound **3** can be derivatized, using different ratios of derivatizing agents to generate analogs with variable R_1 as defined above using a base like TEA or DIPEA in a solvent such as acetonitrile at temperature ranging from 0°C to refluxing to give analogs represented by **4**, **6** and **8**. Subsequent removal of the CBZ groups of compounds **4**, **6** and **8** can give the compounds represented by structures **5**, **7** and **9**.

The present invention discloses methods involve administering (+)-epicatechin, analogs of (+) epicatechin as set out herein, and chemical derivatives thereof. The present invention discloses diseases and disorders that would benefit from increased mitochondrial activity include diseases or disorders associated with mitochondrial dysfunction.

Without being limited by theory, the compounds of the present invention exhibit superior pharmacokinetic and pharmacodynamic properties in comparison to (+) epicatechin.

The present specification is described by way of certain examples meant for illustration. The examples may not be construed to limit the scope of the invention in any manner.

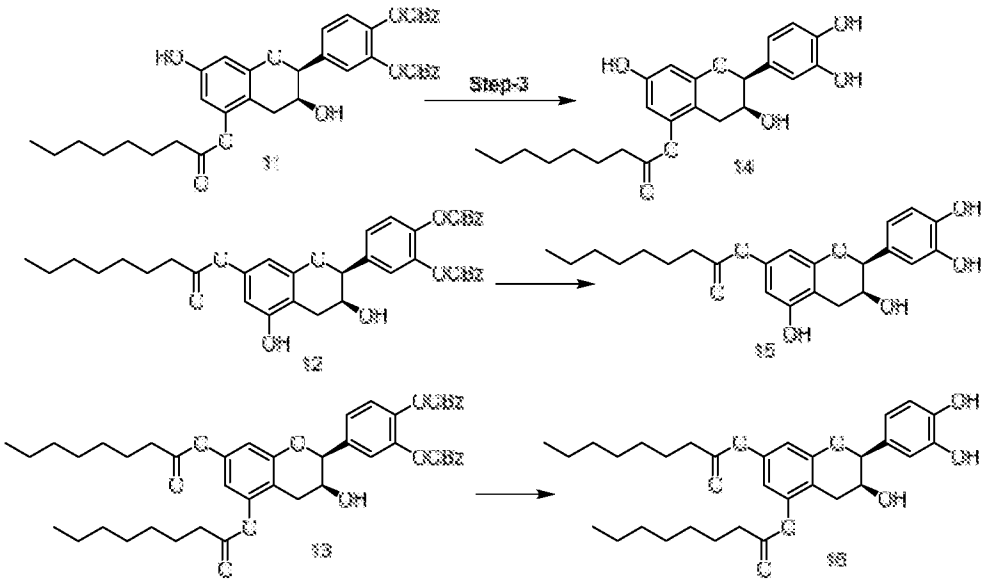
Example 1: Synthesis of Compounds of the present invention



Step-1 : To a stirred solution of **[1]** (0.4 gm, 1.379 mmol) in acetonitrile(40ml) was added triethylamine(0.38 ml, 1.75 mmol) followed by benzyl chloroformate(0.39 ml, 2.75 mmol) at 0°C under nitrogen atmosphere and stirring at this temperature for 90 mins. Reaction was monitored by TLC, three new spots were observed along with the starting compound **[1]**. Reaction mixture was quenched with NH_4Cl solution (5ml) and extracted with ethyl acetate (2x50ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The organic layer was evaporated to afford a light brown solid. This crude product was loaded on to silica gel column and eluted with 10% ethyl acetate/hexane to obtain**[3]** (0.43 gm, 59%)and **[10]**.

Step-2: To a stirred solution of **[3]**(0.4 gm, 0.766mmol) in acetonitrile (40ml) was added triethylamine(0.105 m, 0.766mmol) followed by octanoylchloride (0.124 ml, 0.727 mmol) at 0°C under nitrogen atmosphere and stirring at this temperature for 45mins. Reaction was monitored by TLC. Reaction mixture was quenched with water (5ml) and extracted with ethyl acetate (2x 50ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The organic layer was evaporated to afford a light brown solid. This crude product was

loaded on to silica gel column and eluted with 10% ethyl acetate/hexane to off-white powder **[11](0.110 gm, 22 %), [12]** and **[13]**.



Step-3: To a stirred solution of **[11]** (0.050 g, 0.23 mmol) in ethyl acetate (10 ml), was added 10% $Pd(OH)_2$ (0.015 g) and stirred under hydrogen atmosphere at room temperature. The reaction mass was filtered over celite and the solvent was evaporated out to afford light yellow sticky material. This crude product was triturated with ethyl acetate /n-pentane to afford yellow sticky material as **[14]** (0.025gm, 80%). Compounds **12** and **13** were converted to compounds **15** and **16.**

Example 2: Effect of (+) epicatechin on triglyceride level.

Animals were placed on High Fat Diet (HFD) until they gain more than 20% of Body weight compared with animals on standard chow and reached glycemia levels ≥ 200 mg/dL (usually 4-6 weeks). Animals were randomly assigned to Control (obese group) receiving vehicle only (by gavage): n =12; (+)-Epicatechin – orally by by gavage: n = 10; (-)-Epicatechin – orally by gavage: n = 10.

All animals were treated for 15 days and continued under HFD. The results are presented at Figure 3. Effect on Triglycerides: (+)-Epicatechin (Dose: 0.003

mg/Kg/day shows the same reduction in triglyceride levels as (-)-epicatechin (Dose: 0.1 mg/Kg/day) an improvement of >30 fold.

Example 3: Activity of the analogue of (+) epicatechin of the present invention

The compounds of the present invention were tested for their activity on AMP kinase. The activity on AMP kinase was evaluated by quantitative fluorescent immunoenzymatic assay of AMP kinase phosphorylation status in cultured cells. The 5-AMP-activated protein kinase (AMP kinase) is a key sensor of intracellular energy balance. AMP kinase is activated in response to an increase in the AMP/ATP ratio which can be caused by a number of factors such as muscle contraction, starvation, or hypoxia. AMP kinase is a heterotrimeric protein complex comprising of - (63 kDa), - (38 kDa) and - (38 kDa) subunits. For each subunit, isoforms have been identified (1, 2, 1, 2, 1, 2, 3) which theoretically allow the formation of 12 different proteins. The -subunit contains a serine/threonine kinase domain and the regulatory subunits contain binding sites for AMP and ATP (-subunit) and for glycogen (-subunit). AMP kinase is activated by phosphorylation on Thr-172 within the catalytic domain. AMP binding results in a 2 to 5-fold increase in AMP kinase activity compared to the basal level. Binding of AMP to the -subunit causes allosteric activation of the kinase and induces a conformational change in the kinase domain that protects AMP kinase from dephosphorylation of Thr-172.

BioAssay Systems' cell-based ELISA measure phosphorylated AMP kinase in whole cells and normalizes the signal to the total protein content. The antibody recognizes both -subunits and, thus, can be used for cells from all tissues (human, mouse, rat). This simple and efficient assay eliminates the need for cell lysate preparation and can be used to study AMP kinase regulation in short-term and long-term assays. In this assay, cells grown in 96-well plates are fixed and permeabilized in the wells. AMP kinase phosphorylation (pAMPK) is measured

using a fluorescent ELISA followed by total protein measurement in each well. Compound 1001, exhibits AMPK activity at 1nM.

Example 4: Determination of the pharmacokinetic parameters of the analogue of the present invention.

Female Balb C mice 4 per group after overnight fasting were dosed orally (via gavage) with compound 1 in 5% NMP in normal saline (10ml/kg). Blood was collected by serial bleeding at 0.16hr, 0.5hr, 1hr, 2hr, 4hr, 6hr, 8 h in heparinized tubes. Blood samples were centrifuged at 10,000rpm for 5min. at 4°C to obtain the plasma, which were aspirated into separate labeled tubes and stored at -80°C. 400ng/ml of standard in acetonitrile was used as the drug extraction solvent for extracting drug from plasma. Extraction solvent was added to plasma was vortexed and shaken on shaker for 10 minutes, centrifuged at 10,000 rpm for 10 minutes at 4°C. Supernatant was kept for analysis.

Acetonitrile and plasma calibration curves were generated and percentage of drug recovery from plasma determined. Quantitative analysis was done by liquid chromatography tandem mass spectrometer (API3200 LC-MS/MS). C_{max}, T_{max}, AUC and $t_{1/2}$ were calculated using Graph Pad PRISM version 5.04 and the results were depicted in Table 3.

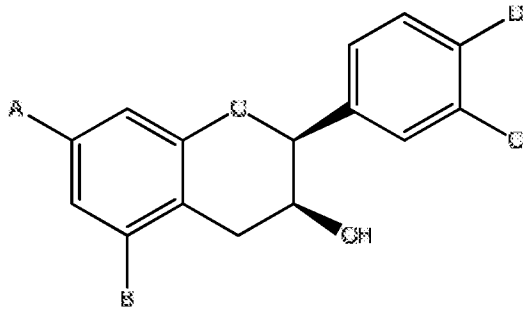
Table 3: Pharmacokinetic parameters of the compounds of the present invention.

	PK STUDY (Oral)		
Compound	**AUC(nM*h)**	**Elimination t1/2 (hr)**	**Dose (mpk)**
(+) Epicatechin	683	2.13	10
1001	2795.70	4.50	10

It may be noted that the compounds of the present invention (1001) are suitable for administration.

We claim:

1. Use of (+)-epicatechin for its utility in Electron Transport Chain.
2. Use of (+)-epicatechin as claimed in claim 1 for its utility in Electron Transport Chain , complex IV
3. Use of (+)-epicatechin for treatment of disorders/diseases associated with Electron Transport Chain
4. Use of (+)-epicatechin as claimed in claims 1 to 3; for its effect on impaired cognition, neurodegenerative diseases such as Alzheimer's or Leigh syndrome, dystonia, sarcopenia, cardiomyopathy of aging or other diseases associated with mitochondrial dysfunction, ischemic vascular disease, immunodeficiency states, ataxia, pulmonary inflammation and fibrosis, infantile encephalomyopathy, epilepsy, Charcot-Marie-Tooth disease, exocrine pancreatic insufficiency, impaired wound healing, growth of cancer cells.
5. Analog of (+) epicatechin of the formula (I),



Formula (I)

wherein A and B are independently OR_1 and C and D are independently OH; wherein R^1 is independently C_1 to C_{10} lower straight or branched chain acyclic or cyclic alkyl, or is selected from the group comprising, hydroxy butyric acid, dichloroacetic acid; phenyl butyric acid; valproic acid.

6. Analog of (+) epicatechin of the formula (I), as claimed in claim 5, wherein B is OR_1 and A, C and D are independently OH; wherein R^1 is independently, C_1 to C_{10} lower straight or branched chain acyclic or cyclic

alkyl, or is selected from the group comprising, hydroxy butyric acid, dichloroacetic acid; phenyl butyric acid; valproic acid.

7. Compounds of formula I as claimed in claim 5, wherein the compound is selected from the group comprising:

i. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl octanoate;
ii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl octanoate;
iii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl dioctanoate;
iv. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl heptanoate;
v. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl heptanoate;
vi. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl diheptanoate;
vii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl decanoate;
viii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl decanoate;
ix. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl bis(decanoate);
x. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diylbis(2-propylpentanoate);
xi. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl 2-propylpentanoate;
xii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl 2-propylpentanoate;

xiii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxy-5-((3-phenylpropanoyl)oxy)chroman-7-yl 4-phenylbutanoate;

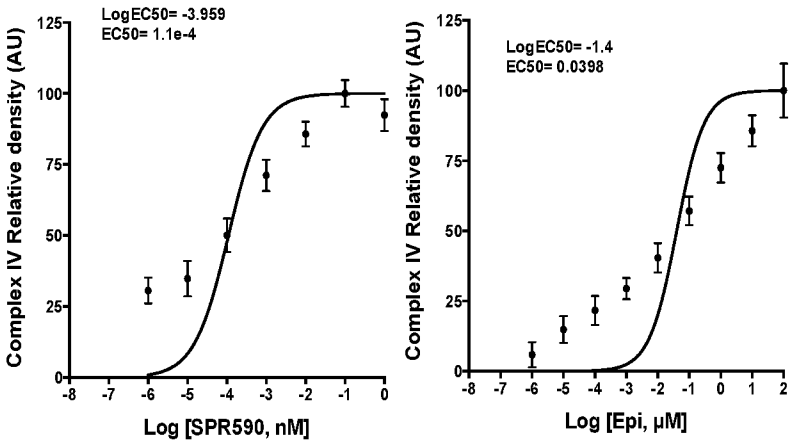
xiv. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl 3-phenylpropanoate;

xv. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl 4-phenylbutanoate;

xvi. (2S,3S)-2-(3,4-dihydroxyphenyl)-3-hydroxychroman-5,7-diyl bis(2,2-dichloroacetate);

xvii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,7-dihydroxychroman-5-yl 2,2-dichloroacetate;

xviii. (2S,3S)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxychroman-7-yl 2,2-dichloroacetate.



Potency ratios (-)-EPI/(+)-EPI = 400

Figure 1

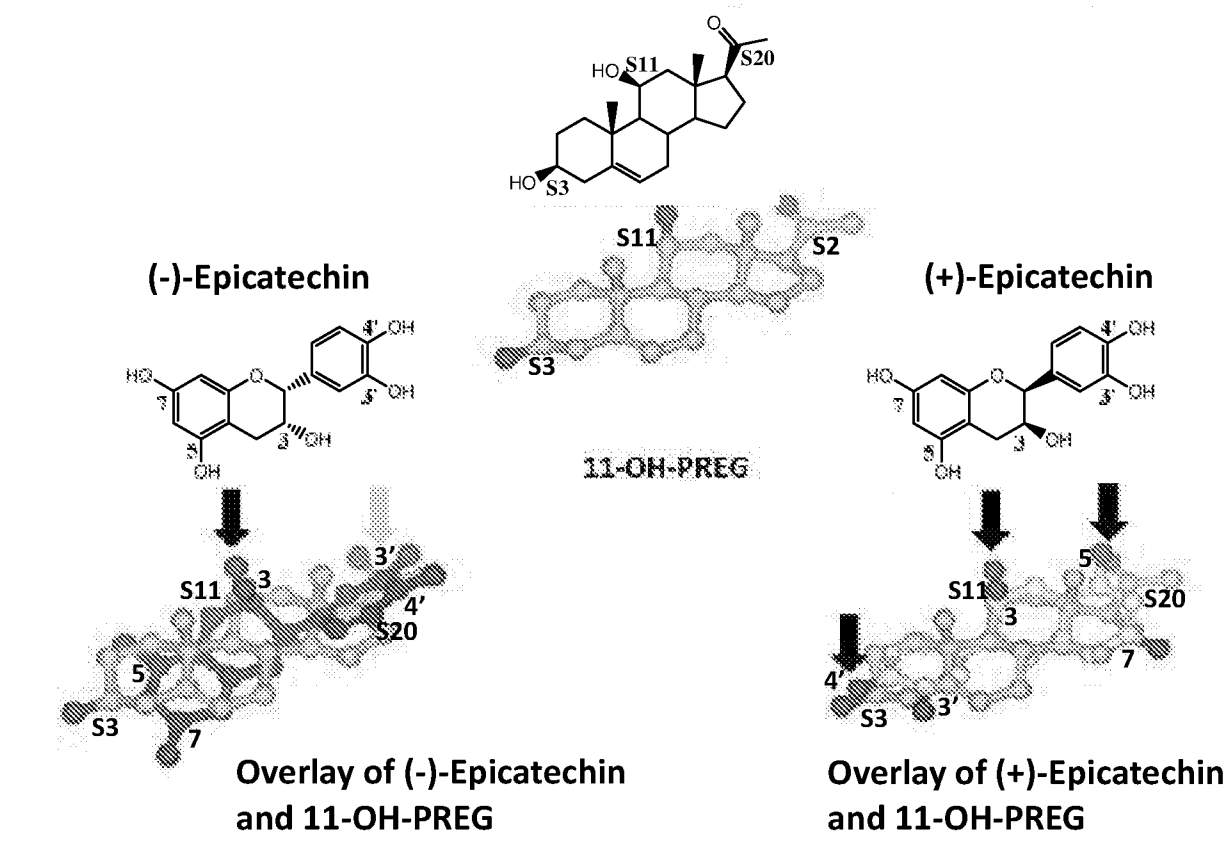

(-)-Epicatechin
(+)-Epicatechin
11-OH-PREG
S11
S2
S3
S20
Overlay of (-)-Epicatechin and 11-OH-PREG
Overlay of (+)-Epicatechin and 11-OH-PREG

Figure 2

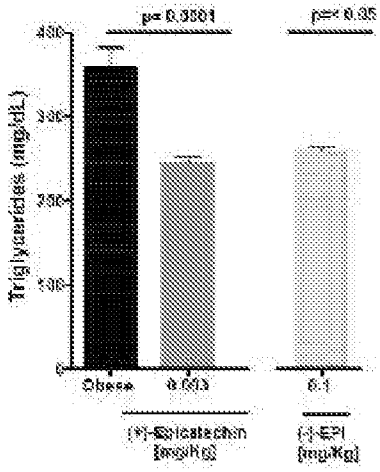

p= 0.3501
p<= 0.05
Triglycerides (mg/dL)
Obese
(+)-Epicatechin (mg/Kg)
(-)-EPI (mg/Kg)

Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/050252

A. CLASSIFICATION OF SUBJECT MATTER
C07H17/06,A61K31/00,C07D311/74,C07D311/62,C07D311/64 Version=2017.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07H, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/0031421 A1 (SPHAERA PHARMA PTE. LTD); 30 Jan, 2014(30-01-2014) abstract, page 1, Para [0006],Para [0028], page 2 Para [0011]-[0015], scheme 2, Page 6-7 Para [0053], compound of formula F2, claims 67-70 and 81-86 .	1-7
Y	WO 2014115174 A2 (SPHAERA PHARMA PTE. LTD); 31 Jan, 2014 (31-01-2014); abstract, page 1, page 11-12, page 17, fig 1, scheme 1-2 page 14-15, page 26, claims 11 and 26-28.	1-7
A	MOINI HADI. ET AL "Bioflavonoid effects on the mitochondrial respiratory electron transport chain and cytochrome c redox state",Redox Report,Vol. 4, No. 1/2, 15 Feb,1999 (15-02-1999),Department of Molecular and Cell Biology, University of California at Berkeley, Berkeley, California, USA; Pages 35-41	1-4

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22-09-2017	22-09-2017
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Kamalesh Kumar Patel Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2017/050252

Citation	Pub.Date	Family	Pub.Date
US 2014031421 A1	30-01-2014	EP 2014031421 A2	04-12-2014
		IN 2013DN07520 A	03-06-2016
		WO 2012101652 A2	02-08-2012
		JP 2014509312 A	17-04-2014
WO 2014115174 A2	31-01-2014	US 2015368223 A	24-12-2015
		EP 2948437 A2	02-12-2015
		IN 2015DN07184 A	01-01-2016
		CN 105026384 A	04-11-2015
		JP 2016507519 A	10-03-2016