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A New Kind of Symmetry in Chemistry and Biology and a Virtual Mirror Intrinsic to Vegetable Tissues Evidenced by Comparative Structural Analysis of Dochi Compounds

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Abstract A unique feature of numerous plants secondary metabolites is the achievement of a stage when their molecule possesses a double set of chiral centers and of chemical functions. Of this reason, we have called them *dochi* (*do* from *double*, *chi* from *chiral*). Three major isomeric types or subgroups can be met inside the group of *dochi*: (A) meso compounds, whose molecule is characterized by a mirror plane of symmetry; (B) The second subgroup of isomers includes chiral compounds whose molecule is formed of two identical halves, and called of this reason *chitwin* (*chi* from *chiral*, plus *twin*). This subgroup had been called also C_2 symmetrical compounds; in fact, they are C_2 symmetrical since they are *chitwin*. The latter compounds are characterized by a plane (or relationship) of *chitwinism*, considered as a new type of virtual mirror (or relationship) showing not the image of the object, as we are used to, but an identical copy of the object. (C) The third subgroup is formed of compounds with asymmetric form, possessing only an identity operation. This subgroup includes chiral compoundsbased on an irregular disproportional distribution of the asymmetric carbons in their molecule, and called of this reason *irrechi* (*irre* from irregular, *chi* from chiral). Here are included only compounds which are chiral and isomers with *meso* and *chitwin* ones. All three subgroups – *chitwin,meso, irrechi* – are characterized by structural and metabolic relationships with other compounds. At the same time, the group of *dochi* includes numerous synthetic compounds, especially of *chitwin* type.

Keywords meso, dochi, chitwin, irrechi, mesaxis, virtual mirror

Introduction

As a result of metabolic transformations taking place in living matter, especially in plants tissues, some compounds arrive at the stage to possess two sets of chiral carbons and of chemical functions. These compounds, forming a significant, ever increasing group, have been called by us *dochi* (*do* from *double*, *chi* from *chiral*), due to their content of chirality. There are two major natural pathways to arrive at *dochi* compounds:

A. The association of identical or similar chemical entities, by strong chemical bonds (covalent, ionic) or by weak ones (hydrogen, van der Waals, etc) is a well known phenomenon in chemistry and biochemistry, which has reached its climax with nucleic acids. This phenomenon has undoubtedly its path of evolution and molecules with doubled structure constitute an important pace of this evolution. The immense majority of *dochi* compounds reaches this state by a dimerization reaction of chiral or achiral monomeric units, possibly followed by some trimming physical-chemical transformations [1-3]. Dimerization process is made in such a manner to block the

process at this stage. In this way are produced: heterocyclic derivatives of 2,5-diketopiperazines, polyprenyl compounds, lignans (nordihydroguaiaretic acids and their derivatives, pinoresinols, secoisolariciresinols), neolignans, cyclobutane derivatives (δ- and μ-truxillic acids), phenols, alkaloids, sesquiterpenoides, coenzymes based on cysteine and cysteamine (coenzyme A, glutathione, both in oxidized state) or on nucleosides, homomeric proteins, lipids (sterol dimers), etc.

B. On the other hand, some *dochi* compounds, characterized by an equal force of representativeness, are produced by indirect biochemical pathways, dimerization reactions being omitted. Of the latter type are some carbohydrates (tartaric acid, mannitol, iditol, etc.) [4-7], unreducing di- and oligosaccharides [8-11], reducing dimer ethers of monosaccharides or their derivatives linked by a spacer [12-14], and a number of amino acids and their derivatives (cystine and its higher homologues, lanthionine, α,ε-diaminopimelic acid, etc.) [15-18].

Structure elucidation of carotenoids [19], their distribution in different species [20] as well as their systematic presentation [21] constitute important pioneering works for chemistry and biochemistry of this important group of dimers.

In this paper classification of *dochi* compounds, their natural distribution and structural variety as well as their correspondence in biology and practical life are presented. This work is in fact a continuation and a development, in ideation sense, of a preceding publication [22].

Classification of *dochi* compounds

The concepts of Kelvin and Prelog [23-26] concerning homo- and heterochirality are usually applied between molecules [27]. The aim of our paper is to disclose the gain of applying these concepts *inside* molecules which are feasible to this process [28]. The *dochi* molecules allow us to establish interesting and important relationships between them as well as inside them. In this way, three types or three subgroups, each one having its subdivisions, can be distinguished in this prominent group of compounds:

(**1**) Symmetric form, possessing S_n symmetry elements. This subgroup includes two major sections: (**A**) *meso* ones, contain compounds whose two sets of chiral carbons are systematically enantiomeric, i.e. their molecule is formed of two enantiomeric halves and the two halves have different priorities. They disclose a fundamental property of matter i.e. the existence of chemical entities having a characteristic internal relationship, usually expressed as the so-called mirror plane of symmetry. According to Kelvin-Prelog theory of chirality, these molecules are internally heterochiral. These compounds are devoid of optical activity, since they possess a content of chirality inside them [29,30], that is made so as to internally annihilate the action on polarized light.

Scientific considerations on all forms of matter include the assessment of symmetry phenomenon. Characterizing the symmetry of a molecule constitutes an important step in predicting its physical-chemical and biological behaviour. One speaks about *meso* type of symmetry not only in chemistry but also in music, in poetry, in sport, in biology, in mathematics, in physics [31-33]. Due to this relationship *via* mirror, of the two halves of a symmetric object, we can afford to know only one half and to reconstitute the other one by desire with the help of a mirror.

There are two aspects concerning the mode of action of the symmetry plane. (**I**) As long as it is drawn between atoms (as is the case of substances with doubled structure), every equivocal situation is avoided; e.g. meso-tartaric acid, galactitol, allitol, galactaric and allaric acids, Cys-Cys and its higher homologues, cyclobutane derivatives, phenolic compounds, alkaloids, sesquiterpenoides, etc. (**II**) When the plane of symmetry has to be drawn through an atom (or a group of atoms) the entity which is cut is imaginarily eliminated, and implicitly the envisaged structure is evaluated as a doubled one; e.g. xylitol [4,34,35], D,L-lanthionine, D,L-α,ε-diaminopimelic acid, etc. (The mirror symmetry plane is a physical instrument and as every instrument has its own force). Probably, such molecules should be called with the prefix pseudo: *pseudodochi*, *pseudomeso*, etc.

For a compound devoid of a visual mirror plane of symmetry (*vide infra*), one should proceed in a rational way: all chiral centers of the envisaged compound are submitted to Cahn-Ingold-Prelog analysis [36,37]. Finally one must find that the compound contains two sets of enantiomeric chiral centers. E.g., (R,S)-zeaxanthin, tunaxanthin

D [(3R,6S,3'S,6'R)-ε,ε-carotene-3,3'-diol], tunaxanthin E [(3R,6R,3'S,6'S)-ε,ε-carotene-3,3'-diol], etc. All homogenous D,L-2,5-diketopiperazines as well as some of their derivatives are part of the latter category: fellutanine A, dimethylfellutanine A, fellutanine C, fellutanine D, dragmacidin B. Also, some species of perhydro polyprenyl derivatives belong to this category: squalane, lycopane, carotane, isorenieratane, renierapurpurane, 1,10-bis(2',2',6'-trimethylcyclohexyl)-3,8-dimethyldodecane, etc.

In fact, *meso* molecules are a kind of reference in this work and many other *meso* compounds will be presented as representatives of different families of secondary metabolites of plants.

(**B**) To this subgroup also belong compounds which are symmetric due to an alternating axis of symmetry, e. g. α-truxillic acid and other similar compounds [35]. We have called this subdivision *mesaxis* and their molecule is also formed of two enantiomeric halves. Symmetric compounds are both precursors and derivatives of some chiral ones.

(**2**) The second subgroup includes dissymmetric forms, possessing only C_n symmetry elements. Of this subgroup, we have focused our attention on the section of chiral isomers whose molecule is formed of two identical halves, and called of this reason *chitwin* (*chi* from *chiral*, plus *twin*). This subgroup had been called also C_2 symmetrical compounds; in fact, they are C_2 symmetrical since they are *chitwin*. Their molecule is formed of two identical sets of asymmetric carbons as well as two identical sets of chemical functions. According to Kelvin-Prelog theory, they are homochiral to one another and moreover they are internally homochiral. Hence, they are super homochiral i. e., they possess a two-fold degree of homochirality. Author's proposal at this step is a relatively new concept, i.e. the virtual mirror (VM) or *chitwinism* mirror, considered as a new type of mirror (or relationship) showing not the image of the object, as we are used to from *meso* compounds and symmetrical articles, but an identical copy of the object. And as a mirror plane of symmetry separates two enantiomeric halves in case of *meso* compounds, a VM (or *chitwin*) plane separates two identical halves in a *chitwin* compound. However, a better manner to disclose the *chitwin* quality is by Cahn-Ingold-Prelog analysis of all chiral centers: one must arrive at a double set of chiral carbons of the same handedness and two identical sets of chemical functions.*Chitwin* phenomenon, VM mirror and plane (or relationship) of *chitwinism* are all new facets of matter disclosed by the reasoning concerning *chitwin* compounds.

Of ten linear hexitols known, four are *chitwin*: D- and L-mannitol, D- and L-iditol, and their aldaric acids are the same. On the other hand, D- and L-arabinitol, the isomers of xylitol, are not *chitwin* but simply chiral. Their 3-keto- and 3-deoxy-derivatives instead are *chitwin*. Of the three types of *dochi* compounds (see below), *chitwin* ones are the most abundant. They are represented in all major classes of secondary metabolites of plants: monosaccharides, amino acids and their derivatives, polyprenyl (isoprenoid) compounds, lignans and similar derivatives (pinoresinols, cyclobutane derivatives, neolignans), phenolic compounds, alkaloids, sesquiterpenoides, coenzymes based on cysteine and cysteamine (in oxidized state) or on nucleosides, homomeric proteins, lipids and even palindromic structures. Furthermore, they are fully represented in synthetic compounds, especially in those designed to manifest distinct physical-chemical and biological properties [38-44]. Numerous examples are presented in this paper.

It is evident that if a compound is *chitwin*, its enantiomer is also *chitwin*, and numerous such pairs can be found in natural materials. Another rule which could be enunciated in this point: compounds containing a double set of chemical functions but only two asymmetric centers, can make up only two types of isomers, *meso* and *chitwin*. E.g. tartaric acid [45], hannokinol [46] 5-keto-D-fructose-1,6-bisphosphate [47], cystine [15], dityrosine dimer [48], zeaxanthin [21], astaxanthin [49], alloxanthin [50], flavuxanthin [51], nordihydroguaiaretic acid [*52],* dihydroguaiaretic acid [*52],* secoisolariciresinol [53], machilin A [54], saururin A [3], enterodiol [55], etc.

In fact, we were preceded by E. Fischer [4,56], by H. B. Vickery[57] and D. Metzler [11], in the knowledge of compounds called by us *chitwin*. Fischer discovered them as derivatives of monosaccharides which by reversion of their ends led to the same product: mannose, idose, threose. In this way, Fischer discovered eight molecules called by us *chitwin* and moreover, he made an inventory of chemical information in this regard and added the enantiomorphic tartaric acids and threitols to the list of the above-mentioned compounds. There were also tentatives to synthesize other compounds of this type, i.e., mannooctitol [58-60[. However, the compound

erroneously called mannooctitol by Fischer and Hudson, could be better called galaoctitol, since it is a *meso* polyol, as galactitol.

On the other hand, Fischer discovered and applied a procedure, probably a natural law, i.e. uniform doubling of a chiral molecule gives rise to a *chitwin* compound. Consequently, he synthesized unreducing disaccharides (trehalose, isotrehalose) and unreducing tetrasaccharides [9,10,61]; they are *chitwin* in the above-mentioned form as well as when the two halves are uniformly linked on a *chitwin* or on a symmetric non-*meso* linker. Fischer as well synthesized 2,5-diketopiperazines of natural amino acids as *chitwin* structures [62].

Vickery defined these compounds as "symmetrical substances which have identical asymmetric structures at both ends of a chain". In this way he evidenced an essential and characteristic feature of these compounds, and moreover he admitted that the problem is extremely important and complex.He got involved systematically in these compounds, including their chemical nomenclature [63]. He used D/L nomenclature, that had been developed by Fischer [4], Rosanoff [64] and Wohl and Momber [65], for their recognition. At the same time, Vickery implicitly admitted that the doubling process for obtaining such compounds can be imagined in two ways:

(**1**) the two identical halves are linked uniformly by themselves, the result being *chitwin* compounds;

(**2**) the two identical halves are uniformly united *via* an atom or a group of atoms; in this case also *chitwin* molecules are produced.

Vickery [57] included α,ε-L,L-diamminopimelic acid in the same category with threitol, tartaric acid and cystine. Our opinion is that α,ε-L,L-diamminopimelic acid presents *chitwin* (L,L- and D,D-) and *meso* (L,D-) isomers.

The subgroup of *chitwin* compounds, is a distinct subgroup of the whole *dochi* one. Their distinct character is conferred by their physical-chemical and biochemical properties [22].

A number of rules and limitations can be evidenced in the construction, and even in defining, of *chitwin* molecules:

i. Uniform doubling of a chiral compound by itself, leads to a *chitwin* structure.

ii. Uniform doubling of a chiral compound on a frame that is already *chitwin*, leads to a *chitwin* structure. Such frames are: trehalose and isotrehalose, secoisolariciresinols, δ- and μ-truxillic acids, etc. Hence, this type includes: trehalose 6,6'-dimycolate, diferulate esters of secoisolariciresinols, glycosides of carotenoids, tetrahydrofuran lignans glycosides, cyclobutane derivatives (δ- and μ-truxilline, stachysetin, monochaetin, sagerinic acid), etc.

iii. Uniform binding of a chiral molecule on the two linkages of a bivalent, symmetrical, non-chiral, non-*meso* ligand produces a *chitwin* structure. Such ligand spacers discovered till now in natural materials are: crocetin, tetrahydro-1,1'-dihydroxy lycopene, diapolycopenedioic acid, (2E,6E)-2,7-dimethyl-2,6-dien-suberic acid, diferulate dimer, dityrosine dimer, etc.

iv. Doubling of chiral compounds on *meso* frames overturns their *meso* status, without making them *chitwin*; they become a kind of hybrid chiral compounds, e. g., α-truxilline [66], (–)-incarvillateine [67], and many others.

v. In dibornyl dimer, dimer bond is formed of one equatorial and one axial linkage, hence this dimer should be considered rather chiral than *chitwin*[68]. Similarly the manner of folding of α-lumicolchicine molecule [69] makes questionable the equivalence of the two halves for *chitwin* quality.

(**3**) The third subgroup is formed of compounds with asymmetric form, possessing only an identity operation. This subgroup includes two major sections: (**A**) chiral compoundsbased on an irregular disproportional distribution of asymmetric carbons in their molecule. Here are included only compounds which are chiral and isomers with *meso* and *chitwin* ones. They have been called *irrechi* (*irre* from irregular, *chi* from chiral) and their subgroup includes a few subdivisions. Of linear hexitols, D-glucitol [L-gulitol; (2S,3R,4R,5R)-hexitol], D-altitol [D-talitol; (2R,3S,4R,5R)-hexitol], L-glucitol [D-gulitol; (2R,3S,4S,5S)-hexitol] and L-altitol [L-talitol; (2S,3R,4S,5S)-hexitol] are illustrative for this type. (**B**) compounds which are simply chiral.

As a conclusion and a consequence of the above reasoning, the existence of four types of compounds possessing a degree of asymmetry (chirality) in their molecule should be admitted (Fig. 1): (**A**) the most abundant subgroup includes compounds which have asymmetric molecular form; they are simply chiral; (**B**) *meso* compounds; (**C**) another subgroup is formed of molecules with dissymmetric form, i.e. *chitwin* ones; (**D**) *irrechi* compounds. All the major subgroups have subdivisions and structural (and sometimes metabolic) relationships with other compounds.

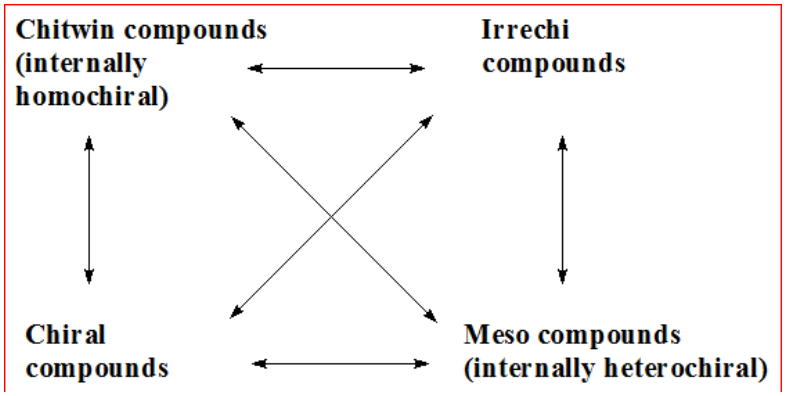


Figure 1: Metabolic and structural diagram interconecting four types (subgroups) of natural compounds having a chirality content in their molecule: chitwin, irrechi, meso and compounds which are simply chiral

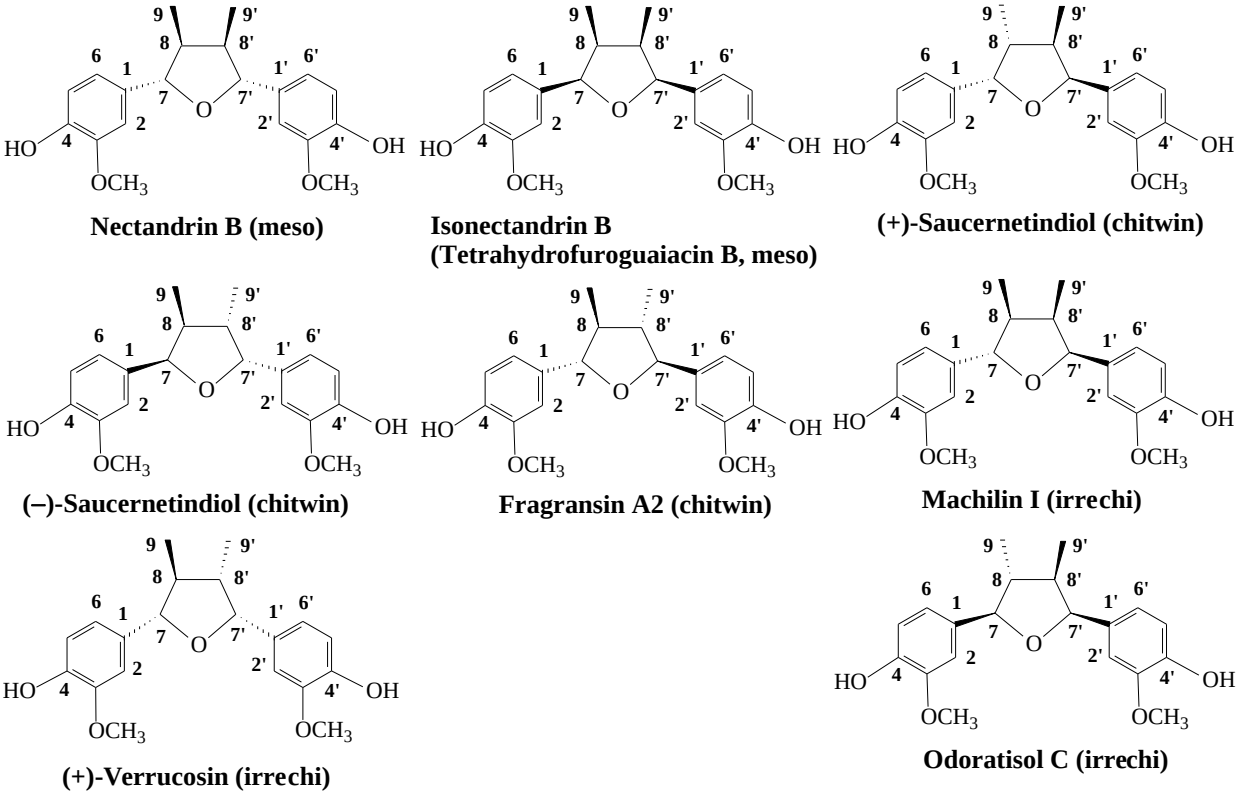


Figure 2: Meso, chitwin and irrechi isomers of nectandrin B

We'll use *meso* isomers along this work as a guide, considering that these isomers should be accompanied by the other two, *chitwin* and *irrechi*. In other words, everyone who knows about *meso* compounds should find out about the other two, as natural extensions of the first one. However, this parallelism between *meso* and *chitwin* characteristics is limited: xylitol is *meso* still D- and L-arabinitol, its isomers, are not *chitwin*, but simply chiral.

The chemical constituents of the four categories are interchangeable with one another (Fig. 1) and all of them are metabolically linked with important achiral compounds: organic acids, keto-acids, amines, etc.

Compounds of *dochi* type, forming three subgroups – *meso*, *chitwin*, *irrechi* – natural compounds or similar synthetic ones [70-72] constitute an impressive number. These compounds had a solid start in the publications of E. Fischer, and then they constantly draw attention and arose enthusiasm of chemists on them. They fascinated chemists equally by their complexity and by their aesthetics, e. g., glabrescol [73], hybocarpone [74], hopeaphenol [75], lomaiviticin A [76-77], baeckeside [78], manassantins [79], epidithiodiketopiperazines [72],teurilene [41], intricatetraol [80], etc. In many instances they constituted a real test for the skill of chemists which proved eager to test their chemical ability by synthesizing such compounds. E.g. hybocarpone and its isomers were prepared by an oxidative dimerization of hydroxynaphthoquinone by a technique of single electron transfer (74).

Our tentative nomenclature discloses the structural variability of secondary metabolites of plants in vegetable living matter. The presence in nature of all three types of isomers (Fig. 2), is probably an uncommon event. Not less surprising is the exclusive natural existence of compounds with 4-10 chiral centers as *chitwin* (intricatetraol, [80]), *meso* [(glabrescol, [73] teurilene, [41])], *irrechi* (quadrigemine C, [81,82]). Below are some applications of our tentative nomenclature. Natural hybocarpone is a *chitwin* compound, and it is characterized by a VM plane (or*chitwinism* plane). Hybocarpone and some of its isomers were produced by chemical synthesis and the following isomers were compared about their relative thermodynamic stability: (2S,3S,4S,5S) (natural compound; *chitwin*), (2S,3R,4S,5S) (*irrechi*), (2S,3S,4S,5R) (*irrechi*), (2S,3R,4S,5R) (*meso*), (2R,3S,4S,5R) (*chitwin*), (2R,3R,4S,5S) (*meso*) [74]. The following conclusions could be drawn: the most stable isomer proved to be the natural one, followed by a *meso* isomer,and the least stable was a *meso* isomer, i. e., the all-cis one. These results are in agreement with a study about lignans: grandisin, a *chitwin* compound, proved to be more stable by 6.5 $kcal \cdot mol^{-1}$ than its all-cis isomer (*meso*), [rel-(7R,8S,7'S,8'R)-3,4,5,3',4',5'-hexamethoxy-7,7'-epoxylignan], due to the hydrogen bonds between methoxy groups in trimethoxyphenyl rings [83]. Manassantin A has been isolated from *Saururus cernuus* L., a plant long recognized for its medicinal value in North America and Korea. The term was coined by Rao and Alvarez [84] from the Sanskrit words "manas" or mind and "santi" or peace, i.e. peace of mind, due to selective neuroleptic activity of manassantin A. The compound surprised since in spite of its biological activities, it was nitrogen-free. Chemists who synthesized manassantin A noticed that it had an "exquisite" symmetry, however they described that symmetry in a different manner [85]. Our presentation, without a dissent with the latter authors' opinion, indicates that manassantin A is a *chitwin* compound, and in this quality it possesses a VM plane (or a plane of *chitwinism*) separating two identical sets of chiral carbons. Beside natural *chitwin* manassantin A, its *meso* and *irrechi* isomers could be synthesized. Quadrigemine C is a representative of a remarkable series of Nb-methyltryptamine-derived plant alkaloids. It was found in *Psychotria oleoides* [86] and in *Psychotria colorata*[87]. The relative and absolute configuration of quadrigemine C was elucidated concomitantly with an isomeric alkaloid, psycholeine, found in the same source [88,89]. The Rabsolute configuration of the two outer quaternary carbons of quadrigemine Cis firmly established, whereas the configuration of the central hexacyclic unit is less secure [81]. According to chemical representations [82], the central partition of quadrigemine C is formed of two enantiomeric entities (a *meso* fragment), while the alkaloid as a whole is *irrechi*.

Many other *dochi* compounds, some of them having relatively complicated structures, have been synthesized: swinholide A, hybocarpone, marinomycin A, epicoccin G, 8,8'-*epi*-*ent*-rostratin B, quadrigemine C, psycholeine [81,82,90].

A relatively less known fact, or at least not fully understood, is the unique contribution of molecules called by us *dochi*, and especially by *chitwin* ones, to the evolution of science. L-(+)-tartaric acid being a *chitwin* molecule, no matter which hydroxyl group is reduced the result is the same, D-(+)-malic acid; the latter can be converted in D-(–)-glyceric acid [91-93]. Based on this experiment, Freudenberg placed (+)-tartaric acid in D-series. On the other hand, (+)-tartaric acid could be synthesized from L-(–)-glyceraldehyde by Kiliani-Fischer chain lengthening [65,93,94]. These chemical transformations, far from being a paradox, strongly demonstrate the versatility of organic chemistry. The experiments of Freudenberg, on one hand, and Wohl and Momber, on the other hand, are not

comparable since their approach is different: Freudenberg just annihilate the chirality of half of the molecule of L-(+)-tartaric acid, while Wohl and Momber reconstitute it from its two identical halves. Monosaccharides which are homogenous in redox terms (linear polyols, aldaric acids) decisively contributed to the elucidation of monosaccharides structure [4,6,56]. The approach of configuration of C-2 by Malaprade reaction has been proposed [95].

Natural distribution and structural variety of *dochi* molecules

A general consideration of natural compounds shows us a consistent illustration of *dochi* molecules within secondary metabolites of plants, by the following families:

1. CARBOHYDRATES: monosaccharides – homogenous derivatives in redox terms: linear polyols and aldaric acids having even-numbered chain, 5-ketohexoses and their 1,ω-diphosphates), unreducing di- and oligosaccharides, reducing dimer ethers of monosaccharides or their derivatives linked by a spacer.

2. AMINO ACIDS AND CHIRAL HYDROXYACIDS: linear diamino-dicarboxylic acids having even-numbered chain; diketopiperazines and their derivatives; homogenous diesters, peroxydes and anhydrides of chiral acids or amino acids, cyclic polypeptides, cyclic di- or polyesters.

3. POLYPRENYL (ISOPRENOID) COMPOUNDS: perhydro isoprenoid hydrocarbons; polyprenyl (isoprenoid) compounds.

4. LIGNANS [tetrahydrofuran lignans, 1,4-diarylbutane (dibenzylbutane) derivatives, furofuran lignans, secoisolariciresinols and their derivatives], NEOLIGNANS, CYCLOBUTANE DERIVATIVES.

5. PHENOLIC COMPOUNDS [96,97].

6. ALKALOIDS [98-100].

7. SESQUITERPENOIDES [101].

8. COENZYMES BASED ON CYSTEINE AND CYSTEAMINE, in oxidized state, or on nucleosides: phosphopantetheine, coenzyme A [11,102-104], glutathione [105-107], ostrerine A [108], nucleoside disulfide [109].

9. HOMOMERIC PROTEINS [110-114].

10. LIPIDS [115-119].

11. PALINDROMES [22,95,120-122].

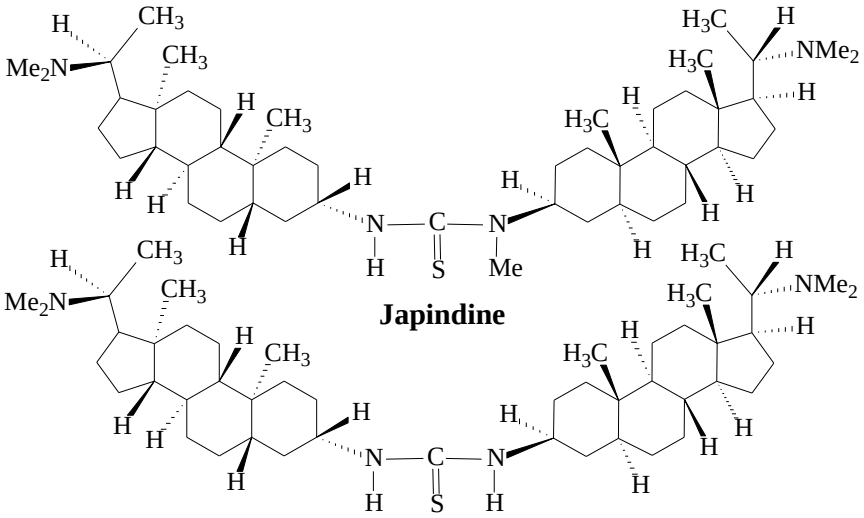
On the versatility of *ent*-compounds

Ent compounds are usually synthetic products which are enantiomers of natural ones. L-Glucose (*ent*-glucose) [123], D-amino acids (*ent*-amino acids) as replicas of DNA coded L-amino acids, *ent*-carboline [124], *ent*-Win 64821 [125], *ent*-chaetocin [126], *sn*-1-glycerol phosphate (*ent*-*sn*-3-glycerol phosphate) [117,118], *ent*-cholesterol [127], *ent*-lithocholic, *ent*-chenodeoxycholic, *ent*-deoxycholic acid [128,129] *ent*-sphingosine and *ent*-psychosine [130], *ent*-adenosine [131], are some representative *ent* compounds. L-Glucose was synthesized in order to be included in a new cerebroside, 1-O-β-L-Glucopyranosyl-N-palmitoyl-DL-sphingosine [123]. If trehalose is synthesized from an equimolar mixture of D- and L-glucose, a *meso* product, α-D-glucopyranosyl-α-L-glucopyranose, would be produced among others. Hence, one can imagine and synthesize a *meso* isomer of carboline, WIN 64821, chaetocin. By using a mixture of cholesterol and *ent*-cholesterol, the synthesis of *meso* derivatives as cholestadiene dimer or as cholesterol diyne [119] is possible. Synthesis of *ent*-adenosine made possible the production of *meso* derivatives of coenzyme A, ostrerine A and nucleoside disulfide (9-(5′-deoxy-5′-thio-β-d-xylofuranosyl)adenine disulfide).

Discussion

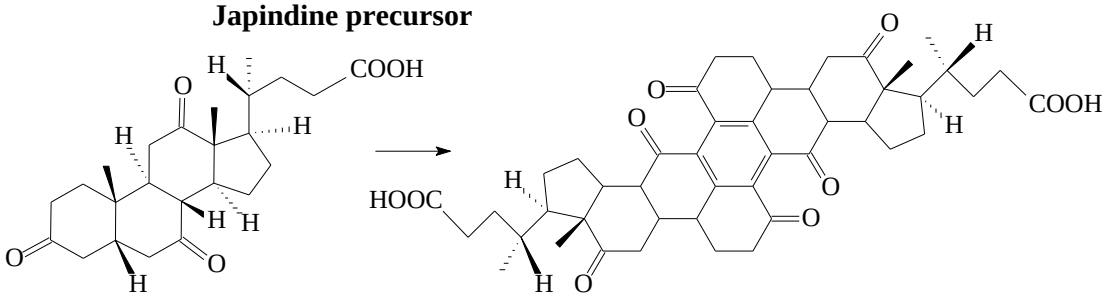
Concerning *chitwin* lipids they are represented especially by sterol dimers and cardiolipin. *Chitwin* sterol dimers are both natural compounds [70,132-134] (Fig. 3) and synthetic ones [70,119,135-141]. Japindine was the first natural sterol dimer known, and it is not a *chitwin* compound, because of the asymmetric methylation of its thiourea residue.

However, if one hypothesizes that the binding of sterol fragments to thiourea precedes the methylation of the latter, that precursor is *chitwin*.

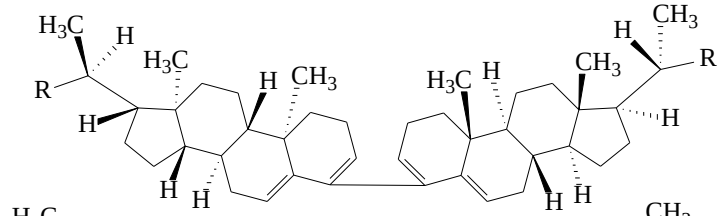


Japindine

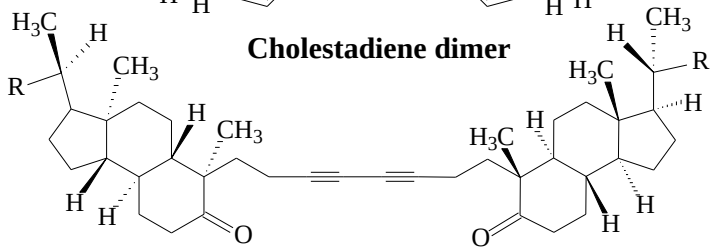
Japindine precursor



Dehydrocholic acid **Dehydrocholic dimer**



Cholestadiene dimer



Cholesterol diyne dimer)

Figure 3: Chitwin natural and synthetic steroid dimers

A distinct representative of lipids very suitable for our discussion is cardiolipin [bis(1,2-diacyl-*sn*-3-glycero-phosphoryl)glycerol or bis(3-phosphatidyl)glycerol] [116]. (In fact, the display of cardiolipin in *sn*-nomenclature is paradoxical: no matter how is glycerol in the middle written, it is both *sn*-1- and *sn*-3-glycerol-phosphate). Our discussion will concern only cardiolipin formed of one or two types of fatty acids [115] uniformly distributed, or

better the product obtained by removing of fatty acids, i. e., [bis(*sn*-3-glycerol-phosphoryl)glycerol]. This species of cardiolipin and its polyglycero-phosphate derivative are neither symmetrical nor *chitwin* but simply chiral. Instead, their derivatives as 3-ketocardiolipin[bis-(sn-3-phosphatidyl)dihydroxyacetone], and 1,3-bis-(sn-3-glycerol-phosphoryl)-dihydroxyacetone are *chitwin*. 3-Deoxycardiolipin, similarly to α,ε-diaminopimelic acid or 3-deoxy-D- or -L-arabinitol, is also*chitwin*. It seems a definitive established rule that phospholipids and glycoglycerolipids of higher organisms are based on *sn*-3-glycerol phosphate. However, a group of archaebacteria contains *sn*-1-glycerol phosphate (*ent*-*sn*-3-glycerol phosphate) as a core structure for their phospholipids and glycoglycerolipids [117,118]. Hence, one can imagine and synthesize a mixed cardiolipin and polyglycero-phosphate ester containing *sn*-3- and *sn*-1-glycerol phosphate, i. e., [(sn-3-glycerol-phosphoryl)-1-glycerol-3-(sn-1-glycerol-phosphate)]. The latter compounds have a *meso* structure and a *pseudoasymmetric* hydroxyl function similar to xylitol [35].

The first argument in favor of the existence of a *chitwin* (bio)chemical forceis the fact that many *chitwin* substances are natural compounds and furthermore considerably represented within the main families of secondary metabolites of plants. As shown above, uniform dimerization of two chiral molecules leads to a *chitwin* compound, while dimerization of two enantiomeric ones produces a symmetrical structure (Fig. 4).

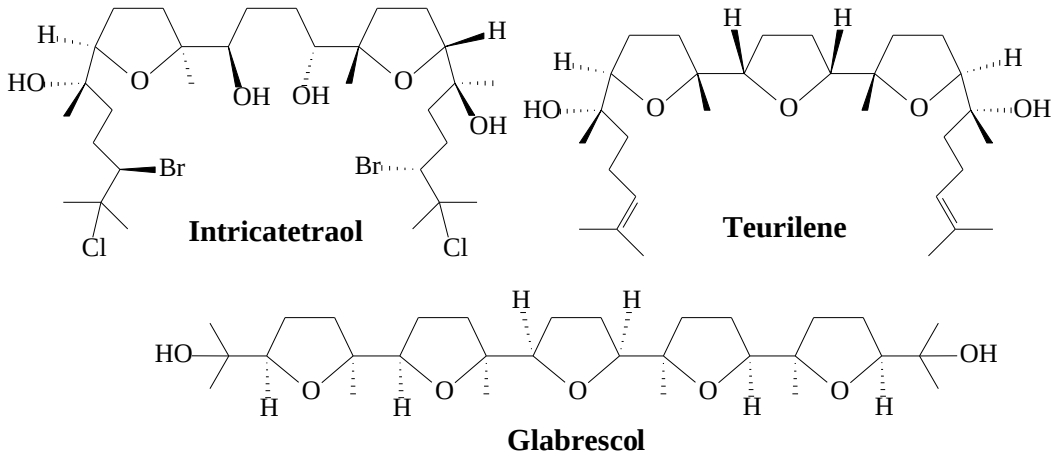


Figure 4: A chiral chemical item formed of two identical halves is chitwin (intricatetraol) and a molecule formed of two enantiomeric halves is symmetric (teurilene and glabrescol)

Both intricatetraol [80] and teurilene [41] are polyisoprenoid compounds formed of six monomeric units: three units are linked head to tail and then two such structures are linked tail to tail. On the other hand, the molecule of intricatetraol is formed of two identical halves, hence it is *chitwin*, while teurilene molecule being formed of two enantiomeric halves is *meso*. Glabrescol is also a *meso* compound [73].

The chiral precursor of *chitwin* compounds could be an amino acid, sterol, nucleotide, ganglioside, (phospho)glyceride, etc. This type of biochemical transformations is well-known in case of diketopiperazines of aminoacids: two different L aminoacids are condensed as mixed diketopiperazines, the result being simply chiral molecules [142]. The latter molecules are then uniformly dimerized producing a *chitwin*construction [72]. E. g., diketopiperazine of Trp and Val is dimerized and sulfurized to form Leptosin K [143].

It is widely accepted that a large number of proteins that are responsible for biochemical and cellular functions exist as dimers or need to be activated by dimerization before mediating certain signaling pathways [39]. Simultaneously targeting both monomeric moieties of the dimeric proteins has shown potential in the development of various therapeutic agents. At the same time, non-protein dimeric molecules, which are generated biogenetically from coupling of two monomeric molecules, might be able to act on both moieties of a dimeric protein. The small dimeric molecules have attracted in recent years great attention for their peculiar structures and biological activities, especially since in dimeric state they are more potent than their monomeric precursors, concerning some important biological activities [144]. Testosterone was dimerized *via* an aliphatic as well as *via* an aromatic residue, the result

being two *chitwin* compounds. Then the affinity of testosterone and its dimers against tRNA were measured and the following order was found: testosterone dimer-aromatic > testosterone dimer-aliphatic > testosterone [43].

Homomeric proteins, when dimeric, are *chitwin* both linked by covalent (Cys-Cys) or ionic linkages. Oligomeric proteins should accomplish a number of conditions, e.g. to contain an even number of monomers, in order to be *chitwin*.

Chitwin phenomenon has an excellent correspondent in biology: phenomena as enantiostyly by plants and antisymmetry by snail species of subgenus *Amphidromus*, provide numerous illustrations (22). In practical life, such objects as gloves, shoes, augers, screwdrivers with the same handedness constitute examples of *chitwin* objects. In his monumental biochemistry textbook, Metzler raised the following question: compare two chromatids coiled with opposite handedness with the existence of snail shells or flowers with both right and left handedness within the same species[11]. And the answer is this one: a pair of two chromatids coiled with opposite handedness, or two flowers or two snail shells with both right and left handedness form *symmetric* systems, while a pair (or an item) of identical objects with the same handedness are *chitwin*.

We have made a systematic and comparative inventory of natural *meso* and *chitwin* compounds, and found out an amazing result: the latter are much better represented concering their structural variety and number (Table 1).

Of the latter Table, we have selected class 3 of *dochi* compounds, POLYPRENYL (ISOPRENOID) COMPOUNDS and exemplified in detail *meso* (Table 2) and *chitwin* (Table 3) subgroups, respectively.

Some important conclusions could be drawn from Tables 1-3. *Chitwin* compounds are the most numerous isomers of *meso* ones, much more abundant than the latter (Table 1). Pinoresinols contain exclusively *chitwin* derivatives. Structural variety of the two types of isomers is much higher in case of *chitwin* compounds, within the same class (compare Table 2 and Table 3). In one subgroup only, guaiaretic acids and derivatives, *meso* isomers are more numerous than *chitwin* ones (Table 1).

Due to exceptional versatility of organic chemistry, the two types of isomers, *meso* and *chitwin*, are interconvertible. Moreover, an enzyme was discovered, an epimerase, which makes two natural isomeric amino acids, L,L-diaminopimelic acid (*chitwin*) D,L-diaminopimelic acid (*meso*) interconvertible [167,168]. By such transformations, mirror plane of symmetry of *meso* isomers becomes VM (or *chitwin*) plane of symmetry and the reverse. The same relationship is between real mirror and VM (or *chitwin* mirror).

Table 1: Comparative abundance of *meso* and *chitwin* compounds of different families of natural products

Class of compounds	Meso	Chitwin compounds
1. CARBOHYDRATES, GLYCOSIDES AND DERIVATIVES	13	37
2. AMINO ACIDS,CHIRAL HYDROXY ACIDS AND THEIR DERIVATIVES	27	82
3. POLYPRENYL (ISOPRENOID) COMPOUNDS	12	69
4. LIGNANS, PINORESINOLS, SECOISOLARICIRESINOLS, CYCLOBUTANE DERIVATIVES, NEOLIGNANS	22	70
4.1. LIGNANS, TETRAHYDROFURAN DERIVATIVES	7	13
4.2. LIGNANS, GUAIARETIC ACID AND DERIVATIVES (1,4-DIPHENYL-2,3-DIMETHYL BUTANE)	7	4
4.3. LIGNANS, PINORESINOLS	-	19
4.4. LIGNANS, SECOISOLARICIRESINOLS	1	16
4.5. CYCLOBUTANE DERIVATIVES	6	14
4.6. NEOLIGNANS	1	4
5. PHENOLS	2	16
6. ALKALOIDS	1	11
7. SESQUITERPENOIDS	2	11
8. COENZYMES BASED ON CYSTEINE, CYSTEAMINE AND NUCLEOSIDES	-	5

9. HOMOMERIC PROTEINS	-	-
10. LIPIDS	-	4
11. PALINDROMES	-	-

Table 2: *Meso* polyisoprenic compounds

Compound	Ref.	Compound	Ref.
squalane;	145	Zeaxanthin-(3R,3'S);	21
lycopane;	146	(3R,3'S)-Astaxanthin	150
carotane;	147	(2R,2'S)-β,β-carotene-2,2'-diol [(2R,2'S)-2,2'-Dihydroxy-β-carotene]	21
isorenieratane;	148	(3R,3'S)-Alloxanthin	151
renierapurpurane;	19	Tunaxanthin D [(3R,6S,3'S,6'R)-ε,ε-carotene-3,3'-diol];	21
1,10-bis(2',2',6'-trimethyl-cyclohexyl)-3,8-dimethyldodecane;	149	Tunaxanthin E [(3R,6R,3'S,6'S)-ε,ε-carotene-3,3'-diol];	21

Table 3: *Chitwin* polyisoprenic compounds

Compound	Ref.	Compound	Ref.
squalane;	145	mactraxanthin;	21
lycopane;	146	ophioxanthin;	157
carotane;	147	mimulaxanthin;	21
isorenieratane;	148	eschscholtzxanthin;	21
renierapurpurane;	19	7,8-dihydro-parasiloxanthin;	158
1,10-bis(2',2',6'-trimethyl-cyclohexyl)-3,8-dimethyldodecane;	149	actinioerythrol;	21
β-Carotene-2,2'-diol;	152	hurghadin;	21
Crustaxanthin-(3S,4S,3'S,4'S);	153	γ,γ-carotene;	159
Crustaxanthin-(3S,4R,3'S,4'R);	153	dimethyl-γ,γ-carotene;	159
Zeaxanthin-(3R,3'R);	21	flavuxanthin;	21
Zeaxanthin-(3S,3'S);	21	tetrahydrobisanhydrobacterioruberin;	21
β-Carotene-4,4'-diol (isozeaxanthin);	49	bisanhydrobacterioruberin;	21
Astaxanthin-(3R,3'R);	153	capsorubin [(3S,5R,3'S,5'R)-3,3'-dihydroxy-κ,κ-carotene-6,6'-dione];	21
Astaxanthin-(3S,3'S);	153	crocin-5;	160
2,2'-Dihydroxyastaxanthin [(2R, 3S,2'R,3'S)-2,3,2',3'-tetrahydroxy-β,β-carotene-4,4'-dione]	21	crocin-3;	161
Nostoxanthin-(2R,3R,2'R,3'R);	21	crocin-2;	160
Zeaxanthin bis-Glcp;	154	crocin;	161
Zeaxanthin bis-Rhap;	155	C. p. 450;	21
Astaxanthin di-lysine (repetare);	156	C. p. 450 di-β-D-Glcp;	21
(6R,6'R)-ε,ε-Carotene;	21	Sarcinaxanthin;	21
(6S,6'S)-ε,ε-Carotene;	21	Sarcinaxanthin di-β-D-Glcp;	21
(6S,6'S)-ε,ε-Carotene-3,3'-dione;	21	Decaprenoxanthin;	162
lactucaxanthin [(3R,6R,3'R,6'R)-ε,ε-Carotene-3,3'-diol];	21	Decaprenoxanthin di-β-D-Glcp;	163
tunaxanthin A [(3S,6S,3'S,6'S)-ε,ε-Carotene-3,3'-diol];	21	Bacterioruberin;	21

tunaxanthin C [(3R,6S,3'R,6'S)-ε,ε-Carotene-3,3'-diol];	21	Bacterioruberin di-β-D-Glcp;	21
Tunaxanthin J [(3S,6R,3'S,6'R)-ε,ε-Carotene-3,3'-diol];	21	okadaxanthin;	21
Alloxanthin;	151	1,2,1',2'-tetrahydro-1,1'-dihydroxy-(di-β-D-Glcp) lycopene;	21
7,8,7',8'-Tetradehydro-astaxanthin;	21	diapolycopenedioic acid-di-β-D-Glcp;	21
[4S,4'S]-4,4'-Dihydroxy-alloxanthin;	21	(2R,2'R)-oscillol;	164
β-Carotene-5,6,5',6'-diepoxide;	21	oscillaxanthin;	21
Violaxanthin;	21	(2S,2'S)-oscillol;	165
auroxanthin-(3S,5R,8R,3'S,5'R,8'R)	21	(2S,2'S)-2,2'-di-(α-L-rhamnosyloxy)-oscillol;	164
auroxanthin-(3S,5R,8S,3'S,5'R,8'S)	21	(2S,2'S)-2,2'-di-(α-L-fucosyloxy)-oscillol;	165
cucumariaxanthin A;	21	sarcinene;	166
3,4,3',4'-tetrahydroxypirardixanthin;	21	astaxanthin bis(β-D-Glcp);	21
cycloviolaxanthin;	21		

Conclusions

1. Numerous natural compounds of vegetable origin have their molecule formed of two sets of chiral carbons and of chemical functions; we have called them of this reason *dochi*compounds (*do* from *double*, *chi* from *chiral*), due to their content of chirality.
2. Three remarkable types of isomers can be distinguished among *dochi* compounds: (**i**) *meso* ones, characterized by a mirror plane of symmetry or of two enantiomeric sets of chiral carbons; (**ii**) *chitwin* (or C_2 symmetrical) i.e. chiral compounds whose molecule is formed of two identical halves; they are characterized by a virtual mirror (VM) plane of symmetry; (**iii**) *irrechi*, that is chiral compoundsbased on an irregular disproportional distribution of the asymmetric carbons in their molecule.
3. Cases where a compound is represented by all three types of isomers are relatively rare.
4. In all families of natural compounds, the number of *chitwin* isomers is much higher than the corresponding *meso* ones. Structural variety of *chitwin* isomers is also higher.

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