Medical Botany
6: Active compounds, continued- safety, regulations

Anthocyanins / Anthocyanins (Table 5I)

O Anthocyanidins (such as malvidin, cyanidin), agrocons of anthocyanins (such as malvidin 3-O-glucoside, cyanidin 3-O-glycoside).

O All carry cyanide main structure (aromatic structure).

▪ Introducing or removing the hydroxyl group (-OH) from the structure,

 The methylation of the structure (-OCH3, methoxyl group), etc. reactants and color materials are shaped.

It is commonly found in plants (plant sap).

O Flowers, leaves, fruits give their colors (purple, red, red, lilac, blue, purple, pink).

O The plant's color is related to the pH of the cell extract.

O Red color anthocyanins are blue, blue-purple in alkaline conditions.

O Effects of many factors in color

 As the pH increases, the color becomes blue.

 the phenyl ring attached to C2;

• As the OH number increases, the color becomes blue,

• color increases as the methoxyl group increases.

O Combination of flavonoids and anthocyanins produces blue shades.

There are 6 anthocyanidins, more prevalent among ornamental-red.

 3 of them are hydroxylated (delfinine, pelargonidine, cyanidin), 3 are methoxylated (malvidin, peonidin, petunidin).

• Orange-colored pelargonidin related.

O A hydroxyl group from cyanide contains less.

• Lilac, purple, blue color is related to delphinidin.

It contains a hydroxyl group more than cyanide.

• Three anthocyanidines are common in methyl ether; From these;

 Peonidine; Cyanide,

Malvidin and petunidin; Lt; / RTI & gt; derivative.

O They help to pollinize animals for what they are attracted to.

Anthocyanins and anthocyanidins are generally anti-inflammatory, cell and tissue protective in mammals.

O Catches and removes active oxygen groups (such as O2 * -, HO *) and prevents oxidation.

O Prevents lipid peroxyl groups (ROO *) and lipid peroxidation (especially nasudine).

Especially cyanide; COX-1, COX-2, α-glycosidase, epidermal growth factor receptor tyrosine kinase (EGF-RTK).

Delfinidin also inhibits EGF-RTK activity.

Aurons / Balconies / Dihydroconcretes (Table 5I)

It is commonly found in plants, especially in the form of glycosides.

O They give color to strawberries and help pollenize.

O The aurons / blades are yellow.

 When they are exposed to alkaline fumes or steam (such as ammonia, cigarette smoke) they turn orange-red.

They are particularly found in the compounds (especially Coreopsis species); They are also found in some other plants.

O Flavanons are isomeric with balconies; In vitro.

 Acid conditions flavanon,

 Alkaline conditions form a calcite.

O Dihydroconcretes are found especially in Gülgiller (Rosaceae) and Fundagillerde (Ericaceae).

O Dihydroconcalation is the reduced form of calcination.

O Extremely bitter flavonoid glycosides, such as neohesperidin, naringin, are converted to dihydrochalcones by hydrogenation in alkaline solutions.

O This leads to significant changes in the tastes of translation; They are 300-1000 times more sweet than sucrose.

In mammals, oxidative phosphorylation breaks the anchor and prevents oxidation.

It inhibits the action of many enzymes, some affect sugar metabolism, others are estrogenic.

O Butein, floretine, isoleucine, pyruvate, oxanate breaks the oxidative-phosphorylation bond.

O Some of the inhibited enzymes are as follows.

 Steroid aromatase: Abissinon VI.

 SDH and tyrosine kinase: Butein.

 MAO: Isolikuiritigenin.

PK: Floretine.

 Iodothyronine deiodinase: Aureusidine, bracheatin, floretine, calconaryingenin, maritimetine, sulfuretin.

O Fluoridzine prevents glucose transport (both from the digestive tract and from the kidneys); It lowers blood sugar.

O Loureyrin B and D are estrogen-receptor agonists.

Xanthones

O are tri-cyclic compounds; Dibenzopiron carries the ring.

O Phenylpropanoid and malonyl-CoA species.

They are of yellow color.

In particular, there are Dutgiller (Moraceae), Hypericaceae (Gentifaceae), Gentianaceae (Gentianaceae), and Sutotugillerde (Polygalaceae).

O There is insufficient information about tasks / roles in the plant.

O In mammals, especially some enzymes (such as MAO, PKC), antibacterial, estrogenic, etc. have many effects.

 α-Mangostin Ca-ATPase inhibits PK, HIV-1 protease activity, is estrogenic and histaminic.

 -Mangostin inhibits HIV-1 protease and PK activity.

 Bellidifolin, demethylbellidifolin, gentiakaulin, isogentisine MAO-A; Noratihidrol PK; Athiourea, isoathiriol, norathiirol prevents xanthine oxidase activity.

 Bellidifolin, mangiferin, swertianolin, isomangostin are antibacterial effects.

Isoflavonoids (Table 5k)

O Subgroup of phenolic substances; Isoflavone parent substance (3-phenylchromone) derivatives.

O Isoflavones, isoflavans, isoflavones, coumestans, pterocarpans, pterocarpens, rotenoids; The last 4 are also known as neoflavonoids.

O Flavanone compounds are liquiritigenin or daidzein or genistein, which is isoflavone compounds,

O isoflavone), formononetin (isoflavone), medicarpine, pisatin (both pterocarpane), rotenone (rotenoid) and coumestrol (coumestan)

Shaped.

O The role of isoflavonoids in plants is not fully known.

O They are considered to respond in response to fungal attack and to form antifungal effects (especially lyclozoflavone, lutein, cisatin, sativan, vestitol, wighteon).

The substances that are formed and effective in this way are known as phytoalexins.

O Some are known as plant estrogens; The estrogenic hormone resembles estrogen in terms of its structure and its dissolution properties.

O Affects the cytoplasmic-estrogen receptors (EST-R) in mammals.

O They are found in plants as a precursor (pre-plant estrogen), i.e. glycosides (daidzein "daidzein 7-0-glycoside", genistin "genistein 7-0-glycoside", glycite "glycitein 7-0-glycoside").

O Glycosides (7-O-glycosides) are weakly active; Because EST-R is less relevant.

 The effects on these receptors are 100-100,000 times weaker than estrogen (estradiol-17β).

 When defeated by animals with normal estrogen levels, they usually act as estrogen antagonists; Therefore, the effects vary depending on the body's estrogen balance.

O This situation also explains why the frequency of breast cancer in people / societies consuming too much plant estrogens or plants containing plant estrogen (such as soy, beans) is low.

They are hydrolyzed in the digestive tract following their beating.

Aglycons (active forms such as daidzein, genistein, glycitein, coumestrol) are released and form estrogenic effects.

These are the major influences in life.

 There are estrogenic effects (daidzein, dihydrodaidzein, dihydrogenysteine, dihydroglycemine, formononethine, genistein, glycitein, coumestrol).

C-glycosides prevent vascular stiffness (genistein 8-C-glucoside, daidzein 8-C-glucoside).

 There are insecticide effects (rotenone).

 Has antimicrobial effects (glabridin, hispaglabridin).

Some inhibit 3β-hydroxysteroid dehydrogenase (3β-HSD), which is synthesized by cortisol and other steroid hormones.

• They are found especially in legumes (Fabaceae / Leguminosae).

O Plants containing estrogenic substances (isoflavones and coumestans) are more important; Some of these plants are:

 Anise (Pimpinella anisum)

 Beans (Vicia faba)

 Kabayonca (Medicago sativa)

 Potatoes (Solanum tuberosum)

 Rice (Oryza sativa)

 Soybean (Soya bean)

 Humulus lupulus (Humulus lupulus)

 Clover (Lotus species)

 As triggers (Trifolium repens, T. pratens)

Terpenoids (Terpenes, Terpenic substances, Table 6)

O In plants, they are prepared via acetyl-CoA (CH3-CO-S-CoA) or acetylthioester (CH3-CO-S-X) which is formed by the action of acetate residues (C2 or CH3-CO-).

O Species from isoprene (C5 or C5H8) units known as five-carbon building blocks; (C5H8) n.

O Isoprene units (also known as isoprenoids) are formed by acetate metabolism via mevalonic acid (MVA).

MVA is formed by the combination of 3 molecules of acetyl-CoA.

Statins (such as atorvastatin, fluvastatin, pravastatin, mevastatin, rosuvastatin, simvastatin) are used to lower blood cholesterol levels in the synthesis of □-hydroxy-□-methylglutaryl-CoA up to mevalonic acid and cholesterol in the synthesis of HMG-CoA reductase.

O active isoprene units in the biological direction;

Dimethylallyl diphosphate (DMAPP; dimethylallyl pyrophosphate) and

Isopentenyl diphosphate (IPP) comes from ester compounds.

□ Two molecules are isomers of each other.

O Terpen; Esasta is formed by the combination of two isoprenyl molecules.

 C10H16 (CH2 = CH-C.CH3 = CH2) fits the formula 2..

 Accordingly, the isoprene molecule is known as hemiterpenes.

It is very important for the growth / development, metabolism and ecology of plants.

O Terpenoids form a significant part of essential oils in plants.

O Extremely powerful fragrance.

O Terpenoids are soluble in oil and are found in the stoplasm of the plant cell.

O Generally extracted from plants with organic solvents (ether, ethyl alcohol, hexane, chloroform, methyl alcohol, petroleum ether).

O According to the number of carbon, they are named as follows.

O Monoterpenoids (10 carbons, C10H16)

 Iridoids (C10H16, two-ring monoterpenoids)

O sesquiterpenoids (15-carbon, C15H24, one and a half terpenes)

 Sesquiterpene lactones (15-carbon, compounds with lactone ring)

O Diterpenoids (20 carbons, C20H32)

O Sesterpenoids (25-carbon, C25H40, two and a half terpenes)

O Triterpenoids (30 carbons, C30H48; triterpenoid saponins)

O Tetraterpenoids (40 carbons, C40H64, carotenoids)

O Polterpenoids (> 40 carbons)

• Monoterpenoids are volatile (boiling points 140-180 ° C); They form a significant part of essential oils.

• Sesquiterpenoids (boiling points> 200 ° C) are also partly volatile.

• Diterpenoids (very volatile), triterpenoids and polyterpenoids are not volatile.

O They are found in volatile oils and dissolved in plants.

O They do not drift with water vapor and do not go into volatile oil.

Monoterpenoids are generally 2-cyclic and 10-carbon (C10) substances made of the 2-isoprene molecule; There are also 2-ring and non-cyclic materials.

Geranyl diphosphatane (geranyl pyrophosphate, GPP; C10) species formed by the association of IPP and DMAPP molecules (via prenyl transferase); In addition to GPP, linalyl-PP (LPP), neryl-PP (NPP), which is the isomers thereof, is also used.

O moving from these 3 building blocks (ie GPP, LPP, NPP);

 Straight-chain hydrocarbons (such as fellandren, limonene, terpinen),

 Alcohol (such as geraniol, linalool, nerol, citronellol),

Aldehydes (such as geranial, neral, citronellal),

 Especially in acetate (geranyl acetate, linalylacetate)

A large number of monoterpenes are formed.

O Small molecular weight, volatile, strongly odoriferous substances.

 Essential oils (fragrant substances, aromatic substances, essences) constitute a significant part of fragrant plants.

O The sesquiterpenoids are partly volatile.

The two groups of substances are also known as small molecular weight terpenoids (KMATs); Up to now, 25.000 KMAT items have been defined.

 KMATs and phenylpropanoids (phenolic compounds) carry similar properties, with different substances.

Most of those mentioned for KMATs are also valid for phenylpropanoids.

 Good solubility in oil, strong odor / volatile / sweet taste.

 They are widely used in perfumery and cosmetics.

• Monoterpenes are well absorbed from the digestive tract and the respiratory tract; They enter the brain.

O The body is especially excreted by respiration and the kidneys.

O These systems are very useful in diseases.

• KMATs are largely colorless and flammable.

• Most optically active; The different isomers have different properties and effects; Organ;

O (+) - carvone mint, (-) - carvone caraway smell.

O (+) - lemon orange, (-) - lemon lemon smell.

• They are found especially in Ballibagilliller (Laminaceae / Labiatae).

- Medicinal effects vary greatly by substance.

It dissolves cholesterol from d-limonene gallstones, prevents tumoral formation, and promotes apoptosis through an unknown mechanism.

O Thujan monoterpenes are GABAA-R antagonists; It causes convulsions and hallucinations.

O Hinokitiol inhibits 5-LOX, 12-LOX, 15-LOX activity; Pain relief and inflammation prevention.

O Pyrethrin-I, -II, synerin-I, -II insecticide is effective.

It blocks the Menthol Ca-channels; Loosen smooth muscles.

O Many of them (such as geraniol, linalool, menthol, cineol) are antimicrobial (fungi, bacteria).

O Iridoids (Iridoids, Monoterpene lactones) are prepared from GPP (C10); Typically bicyclic hemiacetals or lactones.

 Numerous iridoid monoterpenoids can be formed from monoterpenoid geraniol and iridoid logan.

 The hemiacetal structure is unstable; Acid hydrolysis releases the aglycone ring and a highly active aldehyde derivative (colored polymeric form) is formed.

 They form imine-compounds by reacting covalently with proteins.

O They are often found in glycosides and are bitter tastes.

Iridoid glycosides (such as gentiopikroside, harpagoside, catalpol, loganine, swertiamarin) are extremely painful; Increases the salivary secretion and stimulates digestion.

O Radix gentianae luteae glycosides (such as gentiopicroside) are used as appetizing and digestive stimulants in the digestive system disorders (stomach atony, stomach ulcer, pepsin and acid secretion).

 Nepetalactone, iridodiol, neomatatabiol insect repellent / attractant.

 Isovaltrat, valtratum, dirovaltatum is tranquilizer / anxiety remover.

 Baldrin, homobaldrin aldehyde is a mutagenic effect.

 Aukubin is poisonous; To form imine-compounds.

Sesquiterpenoids carry a 3-isoprene molecule; Farnesyl pyrophosphattern (FPP; C15) species formed by the combination of IPP and GPP molecules.

They are either straight chain (such as farnesol, nerolidol), monocyclic (such as abscisic acid, -bisabolene) or 2-ring (such as -kadinen, -selinen).

O Generally bitter and fragrant, partly volatile.

O There are a large number (about 100) of substance groups and / or substances (> 1000) with different effects and isomers.

O Absintin, artabisin (Artemisia absinthium), capsidiol (Capsicum frulescens): It is bitter; They are used as an appetizer.

O Absintin (Artemisia annua): It is effective on malaria and tumors.

O Bisabolol: It is anti-inflammatory and accelerates wound healing.

O Dehydromiyodesmon, dehidrogainon: Toxic to the liver.

O α-Eudesmol: blocks Ca-channels.

O Dehydromiyodesmon, dehidrogainon: The liver is poisonous.

O Germakren-B, α-humulen (Humulus lupulus): It acts as an insect attractant.

O Gossipol: Protein kinases and Ca-dependent protein phosphate inhibit the activity of calcineurin.

O Juvabion: It acts as an insect development regulator.

O Earthing, guaiazulen: Prevents inflammation and oxidation.

O Ptakuiloside (Pterosin B): Carcinogenic.

O Sinnamodial: Vanilloid (capsaicin) receptor agonist.

O Valerenic acid: slows down GABA degradation; Soothing-calming.

Warburganal: Interested in amine and thiol groups in proteins; It is poisonous.

O Zingiberen, kurkumen, patkoulialkol, serden, vetivon: Smell.

O The sesquiterpene lactones are terpenic compounds of 15C carrying five members of the lactone ring.

O Unsaturated 2-, 3-ring compounds; Most of which carry the active methylene group (= CH2).

O They are found in many sub-groups from the chemical side; These groups also carry the -olid (showing the lactone group).

It is usually found in Compound germs (Asteraceae / Compositae).

O Bitter tasting, protective against insect attack, cell poison and anti-tumoral effects.

O Artemisinin; (Plasmodium falciparum), which is resistant to drugs such as chlorokine.

Vernodalin is a protective effect against vernodalol plant insect attack.

O Achillin, by itself, blocks the COX activity of the matrix, removing active oxygen groups.

O Alantolactone, isoalantolactone is an antimicrobial effect.

O Helenalin prevents 5-LOX activity.

 Helenalin-glutathione compound and 11α, 13-dihydrohelenalin acetate GS-S-transferase inhibitor.

O Parthenolide is a serotonin receptor antagonist.

O Picatin and picrotoxin are glycine and GABA-receptor antagonists.

O Santonin is an antelimintic effect.

Thapsigargin stimulates the cells entering the inflammatory response and is a tumor accelerator.

O Thapsigargin, thapsivillosine, trilobolide inhibits Ca-ATPase activity.

Vernodalin is a protective effect against vernodalol plant insect attack.

It also acts as a hapten (antigen).

 In some animals they are responsible for the cross-sensitivities between Parsley (Apiaceae / Umbelliferae) and Compound (Asteraceae / Compositae).

4c. Diterpenoids are 3-ring and 20-carbon materials made from the 4-isoprene unit.

 Geranilgeranil difosfattan (GGPP) is shaped by movement.

 They are common in plants and are biologically active.

 They are not fragrant because they are not volatile.

O Good solubility in oil.

O They are strong flavors.

It is found in the resin part of the plants.

O Usually they are not glycoside.

 Gibberellins act as growth / growth factors in plants and are often used for this purpose.

 Grayanotoxin-I is poisonous; It is found on the leaves of Rhododendron and Kalmia species.

 Stevioside is very sweet; The taste is 100-300 times sucrose; Used as a natural / commercial sweetener.

 Numerous and varied effects (including toxic / harmful effects).

 AS activator: Forskolin (boosts the formation of sAMP).

 Aromatase activity inhibitor: Influx.

 Bitter tasty (glycoside): cafestrol, kahweol, carnosol, columbine, mascaroside

 Insect attractant: Neokembren.

 Plant growth regulator: Gibberellic acid A.

 Protecting against insect attack: Ginkgolides, inflex, columbin.

 Ca-channel blocker: Stevioside.

 Preventing CYP450 efficacy: inhibits the efficacy of caprolactam and kahweol CYP450 in the Kahves; Aflatoxin (2,3-epoxide), thus preventing carcinogenic and other effects.

 Inborn / offspring: Montanol, zoapatanol, portulal, latirol.

 GABAA-R antagonist: Taksodion.

 Glutamate receptor antagonist: Jatrophon.

 Recoil: Forbol esters.

 Cancer inhibitor: Taxol (paclitaxel) and docetaxel tubulin, found in Porsukagaci (Taxus brevifolia), accelerate microtubulin conversion; This effect leads to cancer cell death.

Carcinogens: Forbol esters, ingenol and esters; Co-carcinogenic; That is, they accelerate the development of cancer that has started for other reasons.

Cholesterol enhancer: Raises low-density lipoprotein-induced cholesterol (LDL-cholesterol) in the caffeolol and kahweol plasma, which is in the boiled / unfiltered kaffee; Thus increasing the tendency for vascular stiffness.

 5-LOX inhibitor: Abietan.

Mitochondrial ADP / ATP translocator activity inhibitor: Atrastilocid.

 Na-channels opener: Grayanotoxins; Leading to the opening of tensile-dependent Na-channels, thus impairing depolarization and neuronal conduction.

PAF antagonist: Ginkgolidler.

PK activator: Forbol esters, ingenol and cetyl, resiniferatoxin, tinyatoxin.

 Thrombocyte activity inhibitor: Ginkgolid-A.

 Preventing the development of tumors: Many (such as jatrophon) have this effect.

 Vanilloid receptor (capsaicin receptor) agonist: Resiniferatoxin.

 Anti-inflammatory: Ginkgolidler.

Ingenol, ingenol-3-benzoate, ingenol-3,20-dibenzoate, ingenol-20-hexadecanoate, resiniferatoxin, tinyatoxin, thymalotoxin (PKC activator) which leads to the acceleration of inflammation and tumoral production.

Triterpenoids (Triterpenoid saponins and sapogenins) are 5-ring 30-carbon substances made of the 6-isoprene molecule; Usually in the form of glycosides.

They are synthesized by squalene movement, which is formed by the binding of two FPP molecules to the tail-tail.

O Some of the triterpenoid constituents have fewer carbon numbers.

 Kuassinoids 19-20C,

 Cardenolids 23C,

 Bufadienolidler 24C,

 Limonoids 26C,

 Spirastane-based steroid sapogenins carry 27C.

They are usually found in the form of glycosides; More alcohol, aldehyde, carboxylic acid.

O Colorless, crystallized, high boiling, optically active substances.

O Some are common in plants; This is particularly remarkable in terms of 5-ring triterpenoids.

O Plants are usually found in parts such as resin, latex, shell.

 α- and β-amyrine and acid derivatives (ursolic acid, oleanolic acid, respectively) are found in the waxy part covering fruits and leaves.

O There are many common / different features with steroidal saponins.

 The most important differences between them;

• Triterpenoid saponins in the 5-ring structure (with 30C) are acidic and more commonly found in dicotyledonous plants,

• The steroidal saponins are in the 4-ring structure (27C), they are neutral and are found only in more monocotyledons.

 Similar to steroidal saponins in many other respects (foaming, emulsifying, rattling effect for skin and mucous membranes when rinsed with water).

O Works as a protector against plant insect repellent and microbial attack.

O The main ones and their effects are like this.

Some are bitter (helianthoside-A, quasin, nigakihemiasetala) and some are sweet (abrusosid A-D, glycyrrhizic acid).

O Dammaran, oleaginous and taraksan triterpenoids trypsin and chemotripsin, fire barriers caused by phorbol esters.

O Phytosterols reduce absorption of cholesterol; Low-density lipid.

It prevents the sAMP-FDE effect of the guitar.

It prevents the glycophenes and saikosaponin-A Na-pump.

O Glycyrrhetinic acid (glycyrrhizic acid aglycone) 11? -HSD inhibitor; Thus preventing cortisol from being converted to cortisone.

 When taking too much liquor, mineralocorticoid effect (salt and water retention in the body) occurs.

O Glycyrrhetinic acid (glycyrrhizic acid), oleanolic acid, ursolic acid inhibits PKs.

O -Hederin and oleanolic acid prevent chitin synthase activity.

O Derived cardiac glycosides like cardanolide (digitalin, digitoxin, gitoxin, ouabain, strofantin-K) and bufadienolide (such as hellebrin and sillane) inhibit Na, K-ATPase activity in the heart.

 Increase the contraction power and efficiency of the heart muscle.

O Cucurbitacins (oxygenated triterpenoid) are bitter tasty, antelimintic (ascarid, for strip) and plants are protective against insect attack.

 Kukurbitasin A and D act as insect growth regulators (ecdysteroid) antagonists.

O Limonoids (azadiractin, lemon) are antidote to insect attack.

O Lupeol, -aminine and fatty acid esters thereof inhibit sAMP-dependent PK, serine protease trypsin and chemotripsy.

O oleanolic acid, ursolic acid inhibits DNA polymerase.

It binds to the Tingenon DNA; It prevents DNA-dependent DNA and RNA synthesis.

O The testosterone and androstenedione in the mammals are also found in Pinus silvestris; Some plants also have estrogens.

O The phytoecdyses found in some plants destroy the development of carnivorous insects. Brassinolid (plant growth regulator), ecdison (insect growth regulator) as an antagonist.

O Fitoecdisteroids in humans and animals;

- Accelerates protein synthesis,
- Compliance provider,
- Mutation preventive,
- Cholesterol lowering,
- Immune stimulating,
- Feeder,
- They act as tonic.

Tetraterpenoids (Carotenoids, C40), two molecule GGPP residues.

They contain too many double bonds and are colored.

• The colors are between yellow and red.

 Only carotenoids (C40) are present in this group.

 They are common in all plants.

 Oil-soluble substances.

 Well-known carotenes;

• Either lycopene-based unsaturated hydrocarbons (such as -carotene, -carotene)

• Or oxygenated varieties of them known as xanthophylls (such as lutein, rubixantin, violaxanthin, zeaxanthin).

 Carotenoids function as pollinators (bugs attacking bugs) and seeds (such as weeds, birds attacking bananas).

- One of the most important of the carotenoids is β-carotene.

O Two molecules form retinol (vitamin A, C20).

 Crosetin (in the form of crossover glycosides) found in saffron (Crocus sativus) prevents PK activity.

 Lycopene tomatoes (Lycopersicon esculentum) and orange-red varieties of other fruits.

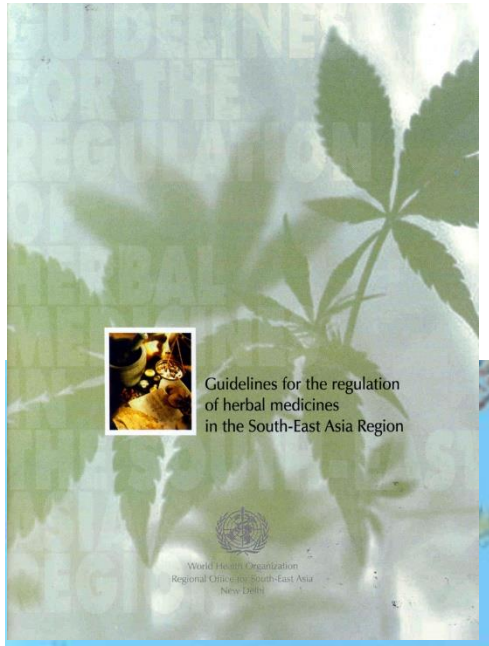
• -carotene with the formation of a closed ring at one end of the lycopene, and -carotene with the formation of a cyclic structure at its two ends.

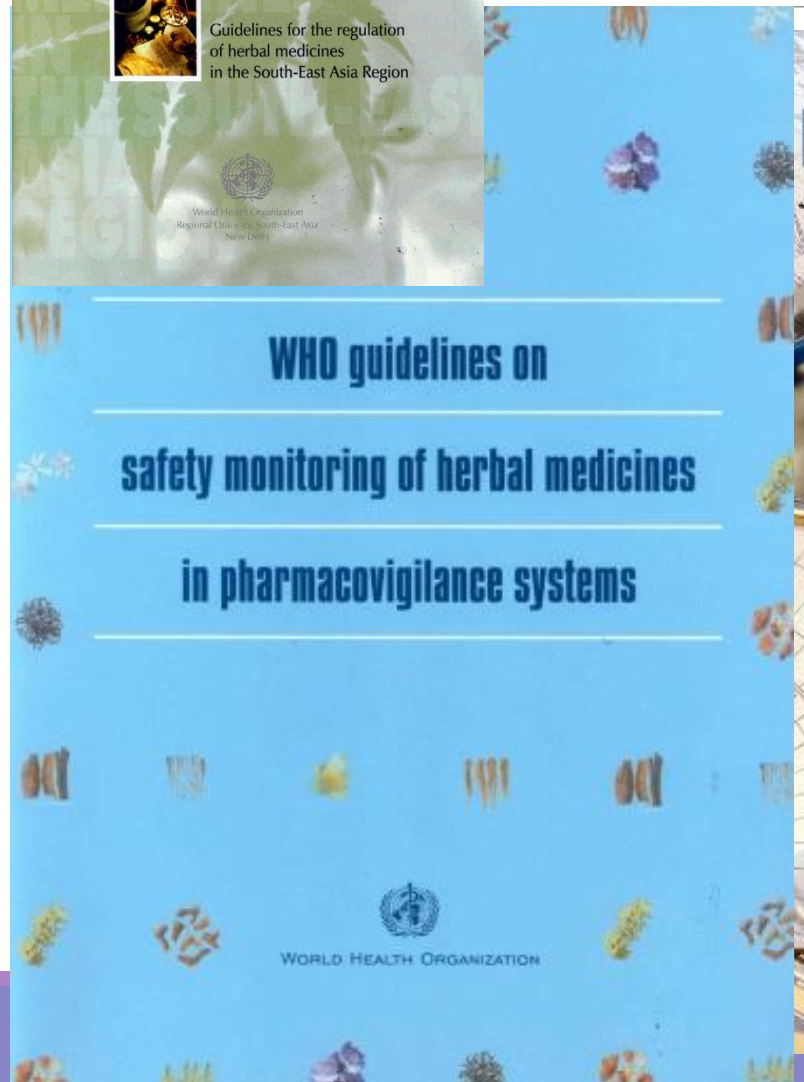
It lowers blood lipids and cholesterol.

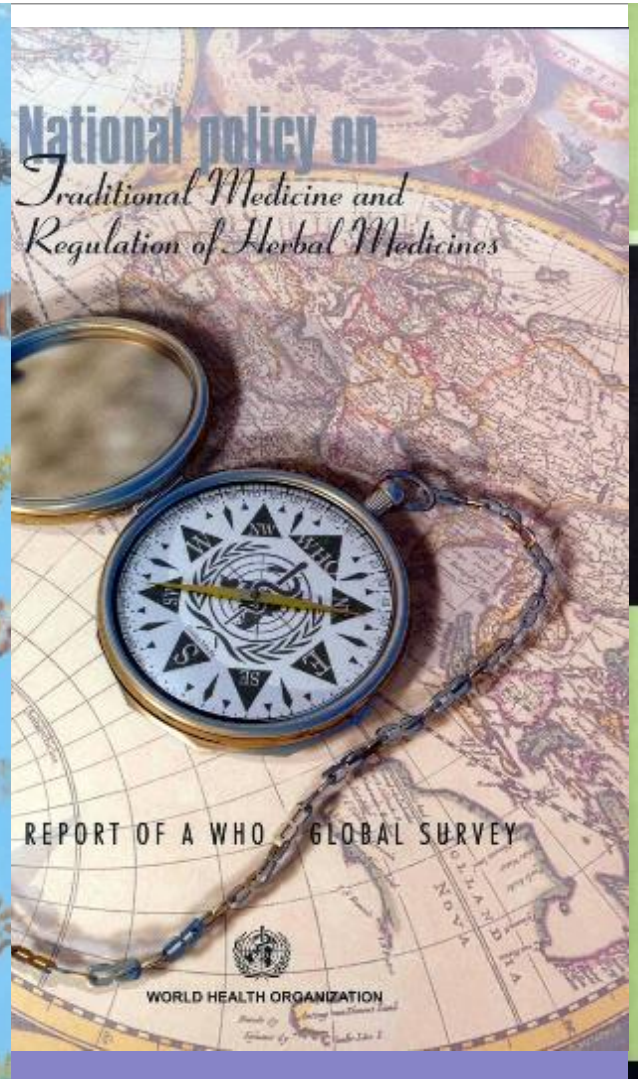
O Remove active oxygen groups.

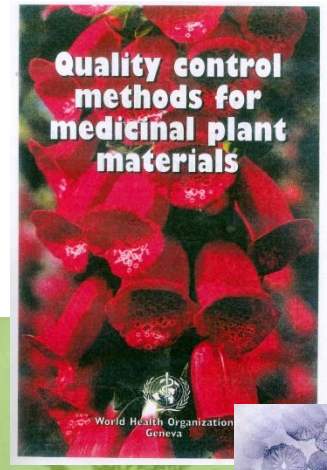
O It is a preventive effect for many types of cancer (urinary incontinence, breast, pancreas, prostate cancer).

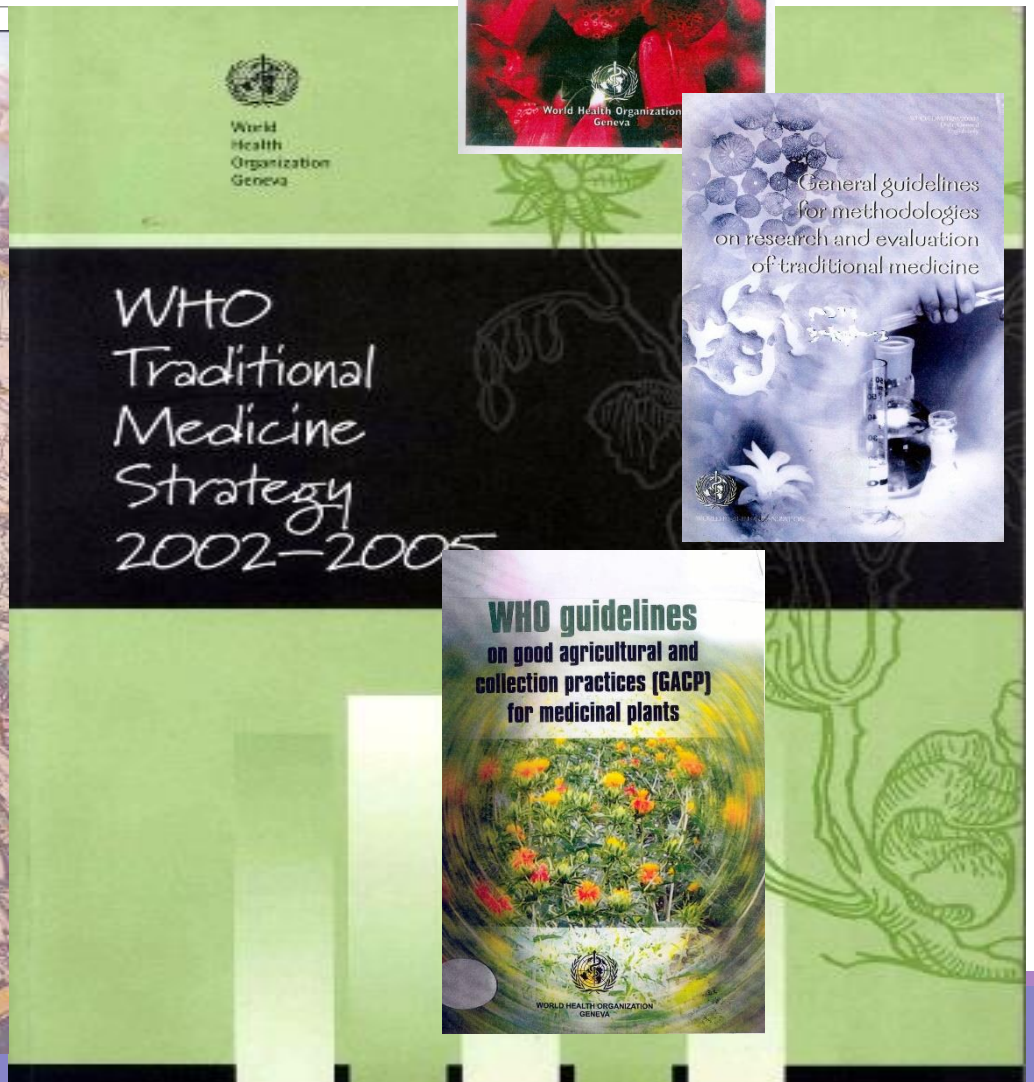
WHO Guidelines











Quality Control Methods for Medicinal Plant Materials

This manual describes a series of tests for assessing the quality of medicinal plant materials. These tests are designed primarily for use in national drug quality control laboratories in developing countries and complement those described in *The International Pharmacopeia*.

It pertains to the following;

Powder fineness and sieve size

Macroscopic and microscopic properties

Determination of ash, extractable matter, volatile oils, bitterness value, hemolytic activity, tannins, pesticide residues, radioactive contamination etc.

AHP: *Authoritative information regarding proper use and manufacture of herbal medicines is lacking.*

30 March 2006
CPMP/QWP/2820/00 Rev 1
EMEA/CVMP/815/00 Rev 1

Guideline on Specifications:

Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products

• In the case of herbal medicinal products, specifications are generally applied to the herbal substance, to the herbal preparation and the herbal medicinal product.

• Specifications are primarily intended to define the quality of the herbal substance/preparation and herbal medicinal product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the herbal substance/preparation and herbal medicinal product.

Macroscopical/microscopical characterization

Includes features which distinguish the herbal substance from potential adulterants and substitutes.

Phytochemical characterization

Analytical data on constituents including constituents with known therapeutic activity as well as compounds suitable as active markers or analytical markers. Includes chromatographic fingerprinting.

Impurities

Impurities can be classified as: arising from starting materials and containers – impurities arising from the manufacturing process – Contaminants such as heavy metals, pesticides, mycotoxins, fumigants as well as microbial contamination – Degradation products in the context of toxicologically relevant impurities and – Residual solvents.

Other Criteria (not elaborated)

Biological variation – Design and development considerations – Pharmacopoeial tests and acceptance criteria – Periodic/skip testing – Release versus shelf-life acceptance criteria – In-process tests – Alternative procedures

Evolving technologies

New analytical technology, and modifications to existing technology, are continuously being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justifiable.

Reference standard

A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. In the case of herbal medicinal products, the reference standard may be a botanical sample of the herbal substance…e.g. a constituent with know therapeutic activity, an active marker or an analytical marker or a known impurity.

Definition of specifications

A specification is defined as a list of tests, references to analytical or biological procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal substance, herbal preparation and herbal medicinal product should conform to be considered acceptable for its intended use.

WHO Guidelines on good agricultural and collection practices (GACP) for medicinal plants

These guidelines are intended to provide technical knowledge on obtaining medicinal plant materials of good quality for the sustainable production of herbal products classified as medicines.

They apply to the following :

Identification, authentication, cultivation and harvest of medicinal plants

Good collection practices for medicinal plants

Common technical aspects of good agricultural practices for medicinal plants in terms of personnel, packaging, storage and transportation.

Relevant issues of ethical/ legal considerations and research

National Policy on Traditional Medicine and Regulation of Herbal Medicine

There is a lack of common standards and appropriate methods for evaluating traditional medicine to ensure the safety, efficacy and quality control TM/ CAM.

In 2001, WHO developed the Global Survey Questionnaire which focused on the following:

General review of policy and regulation of TM/ CAM

Regulation of herbal medicines

Countries need for future WHO support and guidance.

General guidelines for methodologies on research and evaluation of traditional medicine

These guidelines have been developed to promote the proper use and development of traditional medicine and relate to specific issues of methodologies for:

research and evaluation of herbal medicines

research and evaluation of traditional procedure –based therapies

Clinical research norms

Other issues and considerations of ethics, education/ training and surveillance systems.

Safety of Herbal Medicines

Herbal medicines constitute several active compounds

Toxicity studies covers most of the active compounds in the plant (including adverse/toxic effects) Meanwhile, the combination or the inteaction studies are scarce.

Herbal medicines constitute several active compounds

Toxicity studies covers most of the active compounds in the plant (including adverse/toxic effects) Meanwhile, the combination or the inteaction studies are scarce.

Although these are recognized as equally essential attributes of any medicine, safety has taken precedence over proof of efficacy in drug regulation history

“*primum non nocere*” (“first, not do harm”)

the classical version of the Hippocratic Oath that physicians take upon entering medical practice contains a promise that expresses a similar idea (doctors are required to “keep [patients] from harm”).

Although the “*non-maleficence*” maxim has become a central axiom of therapeutics, ethically, it cannot be dissociated from the beneficence principle.

If a clinical benefit superior to that offered by a placebo is attainable by using currently available therapeutic interventions, then not to prescribe the most effective therapeutic option available has a prejudicial impact on the patient's health.

Clinical Assays

Clinical efficacy cannot be presumed on the basis of pharmacological actions described in animal and/or in vitro experiments, nor on physicians'/experts' opinions only.

It has to be demonstrated by adequately designed and conducted phase III studies, or exceptionally by phase II trials.

Clinical Assays

Randomized clinical trials controlled with placebos reveal a number of potential adverse effects associated with drug treatment. If patients allocated to the control group receive a reference medicine instead of a placebo, the incidences of putative adverse effects are compared between the reference and the test drug groups. At any rate, controlled and randomized clinical trials generally provide the best evidence of safety obtainable before marketing.

You can not understand the whole Picture through clinical assays such as

long-term carcinogenicity tests (cancer inducing potential), reproductive and developmental toxicity studies (teratogenic potential)

Rare but severe adverse events arising from interactions with drugs and nutrients, or that occur only in subgroups of patients not represented in the randomized study groups, are likely to be detected only under the actual event of use by a much larger population.

post-marketing pharmacovigilance (PV) is essential for a thorough evaluation of drug safety

Suspicions of ineffectiveness

Uncovering of unexpected severe adverse reactions

often results in the withdrawal of a drug from the market,

The suspicion of reduced effectiveness or even ineffectiveness has seldom prompted regulators to take such drastic action ???

Whether the absence of records of adverse effects is an indication of lack of toxicity depends on the type of toxic effect and the likelihood of observing such an adverse outcome under the conditions prevailing in the traditional usage. Acute symptoms and short- term toxic effects, such as gastro-intestinal disturbances and dermatological effects, are likely to be recognized and associated to herbal medicine. Therefore, the absence of such observations provides some evidence of safety in these particular endpoints. Long-term adverse outcomes, such as cancer, liver and kidney damage, reproductive dysfunctions, birth defects and several morbidities that are more difficult to detect, however, are unlikely to be associated with the popular use of a medicine, unless an adequately designed epidemiology study (preferably, a prospective cohort study) is undertaken

Carcinogenic

Plant species	Constituent	Traditional use	Evidence	
			Humans or animals	Findings
Aristolochia sp.	Aristolochic acid (AA)	Chinese traditional medicine; arthritis, rheumatism, hepatitis, other indications.	Human	Nephrotoxicity, upper tract urothelial carcinoma; meta-analysis: OR = 5.97 (95% CI, 2.78-12.84) for AA-related cancers; TP53 mutations.
Thuja sp., *Artemisia* sp., *Salvia officinalis* L.	α-β-thujone (essential oils)	Traditional medicine, flavoring food additives, absinthe (liqueur).	Rodents	Inhibitor of GABA-A receptor, seizures. Preputial gland and adrenal gland tumors in male rats (no treatment-related tumors in female rats and mice).
Mentha × *piperita* L., *M. longifolia* (L.) Huds., *Nepeta cataria* L.	Peppermint and pennyroyal oils; pulegone	Traditional medicine, flavoring food additives.	Rodents	Hyaline glomerulopathy (male, female, mice, rats); Urinary bladder neoplasms (female rats), hepatocellular neoplasms (mice), osteoma/osteosarcoma (female mice), no tumors in male rats.

Carcinogenic

Sassafras albidum (Nutt.) Nees, *Areca catechu* L., *Piper betle* L.	Sassafras oil; safrole	Traditional medicine, Native Americans and the British, betel quid chewing in Asia.	Human Rodents	Oral squamous carcinomas (humans), hepatocellular carcinomas; DNA-adduct formation and potent rodent carcinogen.
Pteridium sp. (braken), ferns and lycopods	Sesquiterpenois and analogues; ptaquiloside	Food (East Asia and American Indians), food and traditional medicine (New Zealand, the Maoris).	Human Rodents Cattle *in vitro*	Stomach and upper alimentary tract cancers, urinary bladder cancer, neoplasia of several tissues (rodents), thyamine deficiency, acute haemorrhage associated with myeloid aplasia, blindness and retinal degeneration, genotoxicity, teratogenicity.
Symphytum officinale L. (comfrey)	Pyrrolizidine alkaloids	Traditional medicine, Africa, China, Ayurveda, and others.	Human Rodents	Hepatotoxicity, hepatic venous occlusive disease, liver cancer, genotoxicity, DNA adducts.
Euphorbia tirucalli L.	Phorbol esters	Traditional medicine, Africa.	Human Rodents	Burkitt's lymphoma after co-exposure E. tirucalli + Epstein Barr virus, known tumor promoting agent in rodents.

Carcinogenic

Gingko biloba L.	Leaf extract	Chinese traditional medicine, widespread use worldwide.	Human Rodents	Dose-related increase in liver tumors including hepatocellular carcinoma (B6C3F1 mice). Evidence of carcinogenic potential in the thyroid gland (rats, mice); mutagenic (S. typhimurium TA98, TA100, E. coli WPS uvrA/pkM 101, with and without S9).
Rubia tinctorum L. (madder root)	Hydroxyanthra-quinones, lucidin	Traditional medicine and dye. Ayurveda, and in Europe for kidney stones.	Rodents *in vitro*	⊠ liver and kidney malign tumors and DNA adducts, in male and female rats. Mutagenic in S. thyphimurium TA 100 and TA 98 assay, V79 HGPRT assay, malignant transformation assay with C3H/M2 cells.
Senna alata L. (Roxb)	Sennosides	Traditional medicine (Africa, Nigeria, Ghana, Guinea).	Rodents *in vitro*	Mutagenic to S. thyphimurium TA98 and TA 1537 with S-9.
Mixture of plants called Imbiza ephuzwato, Stameta™ BODicare®	(?)	Tradional medicine multi-purpose remedies and tonics (South Africa, The Zulu).	*in vitro*	Plant mixtures were mutagenic in S. thyphimurium TA 98 assay with S9 activation.

Liver toxicity-Hepatotoxicity

Severity of drug-induced liver toxicity (DILI) ranges from mild dysfunction leading to raised serum levels of alanine aminotransferase (ALT) unaccompanied by increases in bilirubin levels and clinical symptoms reversible upon treatment discontinuation, to jaundice and overt hepatic failure that could culminate in liver transplantation or death. DILI can be broadly divided into two types: liver toxicity that depends on the dose and can be predicted by pre-clinical and clinical studies; and an idiosyncratic DILI that is a rare, but severe form of liver damage that occurs only in susceptible individuals (presumably involving immuno-allergic mechanisms) and cannot be predicted by pre-marketing safety studies.

Hepatotoxicity

Traditional herbal medicines associated with human liver injury.

Plant species	Constituent	Clinical/Experimental observations
Larrea tridentata (DC.) Coville (chaparral)	nordihydro-guiarectic acid (?)	Leaves from a desert shrub which are traditionally used in Southwestern USA and Mexico for a variety of therapeuthic indications. Reports of hepatocellular injury and cholestatic hepatitis (jaundice, marked increase of ALT) after weeks of use symptoms generally resolved on ingestion cessation.
Teucrium chamaedrys L., *T. polium* L., T. viscidum Blume, *T. capitatum* L., (germander)	furano-diterpenoids	Europe and Middle East, blossons traditionally used to treat various conditions. Reports of hyperbilirubinemia, anorexia, nausea, marked elevations of ALT, after 2 months of use. Some cases, fulminant hepatitis requiring liver transplantation.
Piper methysticum G. Forst. (kava kava)	piper-methysticin (?)	South Pacific traditional use as a recreational and cerimonial drink. Reports of hepatocellular and cholestasis pattern of liver injury, highly variable cummulative doses and latency periods. some underwent liver transplantation. Idiosyncratic DILI.
Symphytum officinale L. (comfrey) *Senecio* sp., *Heliotropium* sp., *Crotalaria* sp.	pyrrolizidine alkaloids	Europe, Asia, South Africa, USA, Jamaica, worldwide traditional medicine. venous occlusive disease, abdominal pain, ascites, slight jaundice and hepatomegaly (similar to Budd-Chiari Syndrome).
Atractylis gummifera L.	atractylosides, gummiferin	Mediterranean region use as antipyretic, emetic, diuretic, chewing gum. Acute hepatitis, nephrotoxicity, hepatorenal failure.
Callilepsis laureola DC.(Impila)	atractylosides	South Africa use in Zulu traditional medicine. Acute liver and kidney injury, abdominal pain, diarrhea, vomiting, high mortality.
Chelidonium majus L.	celandine	Europe and temperate regions of Asia. Used to treat dyspepsia, biliary colic, cholelithiasis. Several case reports describing acute liver injury, moderate elevations of ALT, marked cholestasis, recovery after herbal medicine discontinuation.
Mixture of plants (Herbalife® products)	(?)	Widespread use as food supplement. Case series of fulminant liver failure, hepatocellular damage, veno-occlusive disease and cholestasis.+

+The comment of Herbalife® manufacturers on the report of DILI cases possibly associated to their product is found (2013) and authors' reply in Reddy and Bunchorntavakul (2013).

Interactions with Conventional Medicines

Herbal medicines are often used concomitantly with conventional drugs, making potential pharmacokinetic interactions a cause for concern.

Herbal drug co-administration with medicines of narrow therapeutic indices (*e.g.*, digoxin, warfarin) raises even deeper safety concerns

Example: St. John's wort

* St. John's wort (sarı kantaron), an herbal antidepressant, is possibly the most notorious

* potent inhibitor of CYP3A4, and when co-administered with drugs metabolized by this enzyme, it decreases their clearance and increases their plasma concentrations (AUC).

* Because St. John's wort also induces the expression of CYP3A4 and the transmembrane transporter protein PgP (P-glycoprotein) in the liver and intestines, previous and repeated administrations have opposite effects; enhancement of clearance and decrease in AUC.

The kinetic and clinical effects of a number of drugs that are substrates for CYP3A4 are altered by St. John's wort, and these drugs include cyclosporine, midazolam, oxycodone, methadone, imatinib, finasteride, bupropion, tracolimus, digoxin, atorvastin, and verapamil, among others.

Pharmacokinetic interactions of herbal medicines and edible plants with conventional drugs.

Plant species	Constituent	Kinetic interactions	Clinical/Experimental findings	References
Gingko biloba L.	flavonoids; terpene lactones (ginkgolides)	CYP3A4 (ind/inh), 2C9, 2C19 (ind, HD); P-glycoprotein (ABCD1) (ind/inh).	↑ CYP2C19-hydroxilation of omeprazole, ↓ plasma levels of omeprazole, ↓ plasma levels and AUC of midazolam.	Chen et al., 2011; Hermann and von Richter, 2012; Li et al., 2013.
Allium sativum L. (garlic)	alliin, allicin; flavonoids; isoflavonoids; terpenes	CYP2E1 (inh), pgP (ABCD1) (ind).	↓ AUC saquinavir.	Gurley et al., 2002; 2005; Hajda et al., 2010.
Silybum marianum (L.) Gaertn. (milk thistle)	flavolignans, silymarin mixture	CYP3A4 and 2C9 (inh), UGT1A1, 1A6, 1A9, 2B7, 2B15.	↓ clearance: metronidazole and hydroxymetranidazole, ↑ AUC of losartan.	Chen et al., 2011; Sridar et al., 2004.
Hypericum perforatum L. (St. John's wort)	hypericin, hyperforin; favonoids; biflavonois	CYP3A4 and 2B6 (ind / inh); CYPC19, UGT, GST, PgP (ABCD1) (ind).	↓ (ind) / ↑ (inh) AUC: cyclosporine, tracolimus, imatinib, warfarin, digoxin, verapamil, nifedipine, finasteride, glicazide, theophylline, bupropion, amitriptyline, midazolam, atorvastatin, nevirapine, indinavir, methadone, omeprazole and others.	Chen et al., 2011; Li et al., 2013.
Citrus × paradisi Macfad. (grape fruit juice)	Narigin (?)	CYP3A4.	↑ AUC: dihydropyridines, terfenadine, saquinavir, cyclosporin, midazolam, triazolam, verapamil, lovastatin, cisapride and astemizole.	Bailey et al., 1998; Fuhr, 1998.

ind: enzyme induction (previous and or repeated administration); inh: enzyme inhibition (concomitant administration); HD: high doses; UGT: UDP-glucuronosyltransferases.

Drug Interactions

Activity and/or expression of drug-metabolizing enzymes and transmembrane transporters, and by doing so, they can modify drug elimination, metabolic activation (*i.e.*, conversion of a precursor into its active metabolite), pre- systemic clearance, bioavailability, and kinetic parameters such as AUC, Cmax and Tmax.

All these effects may eventually lead to changes in toxicity and/or clinical efficacy of conventional drugs. Therefore, knowledge of the potential of herbal medicines to inhibit (when co-administered) and/or induce the expression (after previous and/or repeated administration) of key drug-metabolizing enzymes (*e.g.*, CYP3A4, 2D6, 2C9, 2C19, 2A6) is of the utmost importance for safety when used in conjunction with conventional drugs.

Pre-clinical and clinical evaluation of toxicity and post-marketing pharmacovigilance.

Post-marketing pharmacovigilance is essential to bring problems of effectiveness and rare adverse effects (*e.g.*, idiosyncratic DILI and immuno-allergic reactions),

the occurrence of which is not anticipated by experimental and clinical studies

Prior to 1984, there were no regulations for herbal products. Crude drugs were sold in "Akthar" shops, where no special training was required for the persons responsible. In 1984, the Fifth Symposium on Crude Drugs, held in Ankara, was the first step for regulatory action on herbal products.

A resolution of the symposium described the situation of herbal products, presented ideas for the solution of problems, and recommended a specific regulation for herbal products

A regulation was published by the Ministry of Health on 1 October 1985 and included a list of plants allowed to be sold in the Akthar shops, mainly crude herbs and their parts. The sale of poisonous plants such as Belladonna or Bulbus Scillae was not permitted. Since 11 March 1986, special permission by the Ministry of Health is required to open an Akthar shop.

The Recall of Pharmaceutical and Medical Drugs, Substances, Compounds and Herbal Preparates Regulation (*Sağlık Bakanlığı Farmasötik ve Tıbbi Müstahzar, Madde, Malzeme, Terkipler ile Bitkisel-Preparatların Geri Çekilmesi ve Toplatılması Hakkında Yönetmelik;* Official Gazette No. 19196, dated 15 August 1986) (Recall Regulation on Pharmaceutical and Medical Drugs) outlines principles which apply to recalling medicinal products found to be defective or faulty in terms of consumer health and safety, or which fulfill other legislative reasons for recall.

A regulation on licensing herbal products which have any medicinal indication claim on the label was published 2 March 1995

The basic principles of these regulations are the following:

1. Each Akthar shop must be registered by the local branch of the Ministry of Health to be able to sell herbs. Promotion of these products with health claims is strictly forbidden.

2. According to the registration procedure, there are three classes of herbal products:

   - products from plants without a risk potential for human health and without any health claim on the label, which are handled according to the food regulation;
   - herbal products presented in pharmaceutical forms such as tablets or capsules, which must be registered by the Ministry in the same way as medicinal products, and require a complete documentation; and
   - herbal teas with health claims on the label, for which registration by the Ministry is needed, but the documentation required is limited to quantitative formulae, specifications, quality control methods, summarized production method, and a sample of the package insert [100].

With the increasing importance of products of plant origin, the Ministry of Health decided to establish a separate commission for registration of herbal medicines, the Herbal Committee which consists of 3 pharmacognosists, 2 technologists, 1 pharmacologist and 1 toxicologist.

Medicinal products are only permitted to enter the Turkish market if they have a valid marketing authorisation.

Marketing authorisations are issued in accordance with the Regulation on Licensing of Medicinal Products for Human Use (Official Gazette No. 25705, dated 19 January 2005 (Licensing Regulation on Medicinal Products).

The various requirements and conditions for medicinal products are regulated under different pieces of legislation.

Directive No 2004/24/ EC	Implementing Regulation on the Simplified Licensing of Traditional Herbal Medicinal Products	To audit the traditional use of the products whose traditional use is authenticated bibliographically or through expert evidence and to prevent public health from their adverse effects by defining them as products containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.	The Implementing Regulation, which had been projected to be published in 2009, was published in the Official Gazette no. 27721 of 6 October 2010 and entered into force as the "Implementing Regulation on Traditional Herbal Medicinal Products".

From the Ministry of Health:

Regulation on the Registration of Medicinal Products for Human Use

SECTION ONE

Objective, Scope, Legal Basis and Definitions

3. HERBAL MEDICINAL PRODUCTS

Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.

Module 3

The provisions of Module 3, including compliance with monograph(s) of the European Pharmacopoeia, shall also apply to the registration of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.

The following aspects specific to herbal medicinal products shall be considered:

1. Herbal substances and herbal preparations:

For the purposes of this Annex, the terms "herbal substances and preparations" shall be considered equivalent to the terms "herbal drugs and herbal drug preparations", as defined in the European Pharmacopoeia.

With respect to the nomenclature of the herbal substance, the binomial scientific name of the plant (species, variety and author) and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (species, variety and author) and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

For the purpose of documenting the section of the structure for herbal substance(s) and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula and the relative molecular mass) as well as other constituent(s) shall be provided.

For the purpose of documenting the section on the manufacturer of the herbal substance, the name, address and responsibility of each supplier (including toll manufacturers) and each proposed site or facility involved in production/collection and testing of the herbal substance shall be provided, where appropriate.

With respect to the elucidation of the structure and other characteristics of the herbal preparation, information on the phyto-chemical and physicochemical characterization and biological activity if necessary, shall be provided.

The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance(s) and herbal preparations where applicable shall be provided.

With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopaeial substances.

Justification for the specifications of the herbal substances and herbal preparations where applicable shall be provided.

Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.

2. Herbal Medicinal Products

With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.

- GTHB Türk Gıda Kodeksi "Takviye Edici Gıdalar Yönetmeliği"nde (02.05.2013 tarih, 28635 sayılı RG)
  - "takviye edici gıdalar; normal beslenmeyi takviye etmek amacıyla vitamin, mineral, protein, karbonhidrat, lif, yağ asidi, amino asitler gibi besin ögelerinin veya bunlrın dışında besleyici veya fizyolojik etkileri bulunan bitki, bitki ve hayvan kaynaklı maddeler, biyoaktif maddeler ve benzeri maddelerin konsantre veya özütlerinin tek başına veya karışımlarının kapsül, tablet, pastil, tek kullanımlık toz paket, sıvı ampul, damlalıklı şişe ve diğer benzer sıvı veya toz şekillerde hazırlanarak günlük alım dozu belirlenmiş ürünler" şeklinde tanımlanmıştır.
  - Bu tanıma dayanarak Türkiye'de satışı yapılan ve Bakanlık tarafından "takviye edici gıda" olarak kabul edilen ama aslında çoğu "bitkisel ilaç/bitkisel tıbbi ürün" olarak kabul edilmesi gereken bitkisel ürünlerin izinlerini vermektedir.

SB tarafından yayımlanan Geleneksel Bitkisel Tıbbi Ürünler Yönetmeliği (06.10.2010 tarih, 27721 sayılı RG) ile "insan sağlığını koruyucu ve tedavi edici etkileri olan ve geleneksel bitkisel tıbbi ürünlerin endüstriyel olarak üretilmesi veya ithal edilmesi ile ilgili başvuruların değerlendirilmesi ve ruhsatlandırılması" yapılmaktadır.

GTHB tarafından yayımlanan "Takviye Edici Gıdalar Yönetmeliği"nde ürünün piyasaya arzında;

- İzlenebilirlik (hammadde temini-üretim-dışalım-işleme-piyasaya arz ile ilgili tüm aşamalarda karekod uygulaması),
- İhtiyati tedbirler (üretim-dışalım-işleme-piyasaya arzın durdurulması),
- Resmi kontroller (17.02.2011 tarih, 28145 sayılı RG; Gıda ve Yemin Resmi Kontrollerine Dair Yönetmeliğe göre),
- Etiketleme (29.11.2011 tarih, 28157 sayılı RG, 3ncü Mükerrer; Türk Gıda Kodeksi Etiketleme Yönetmeliğine göre) esas alınmıştır.

Tracebility

Precautions

Official controls

Labelling

Due to uncertainities in the regulation

Products licensed by Ministry of Health are marketed in pharmaceutical warehouse (Retail/wholesale)

Similar product (even derived from the same plant) licensed by the Ministry of Food, Agriculture and Livestock are sold in the company's own shop or other food markets, companies own warehouses, internet (www.abc.com) and/or othwe web services, or other retail houses.

Veterinary Herbal Medicine Regulations

Currently 18 veterinary herbal preparations are licenced.

Plant/plant parts to be used in animal of food origin are standardizied by the MFAL by the regulation (29.04.2011, 27919) in Annex 2.

Licensed Veterinary Medicinal Products are given in Annex 5.

S

Since these products have emerging importance due to organic farming, information for veterinary herbal medicines are also given under the legislation of organic farming as well.

Türkiye'de Organik Tarımın Esasları ve Uygulanmasına İlişkin Yönetmelik (18.8.2010 tarih, 27676 sayılı RG)

"Hayvan Sağlığı ve Veteriner Müdahalesi" Section 18 is as follows.

ç. Organik hayvancılıkta veteriner hekim gözetiminde veteriner tıbbi ürünlerin kullanım usul ve esasları şunlardır:

1. Tedaviye alınan hayvan türü üzerinde tedavi edici etkisinin bulunması ve tedavi koşullarına uygun olması kaydıyla kimyasal sentezlenmiş veteriner tıbbi ürünler dışında allopatik ürünler, fitopatik ürünler, bu Yönetmeliğin Ek-5'inin 3 üncü bölümünde ve Ek-6'sının 1 inci bölümünün 1.1 bölümünde listelenen ürünler kullanılır. Ayrıca, tedavide homeopat tedavi yöntemleri de uygulanır.

2. Yukarıda bahsedilen maddelerin kullanımının hastalıkla veya yaralanmayla mücadelede yetersiz kalması durumlarında ve hayvanın acı çekmemesi için tedavi amacı ile kimyasal bileşimli ilaçlar veya antibiyotikler yetkilendirilmiş kuruluşun izni ile kontrollü olarak kullanılır.

3. Kimyasal olarak sentezlenmiş veteriner tıbbi ürünler veya antibiyotikler, hastalık önleyici uygulamalar için kullanılamaz.

ç. Organik hayvan yetiştiriciliğinde, hayvanların genetik yapısı değiştirilemez ve genetik yapısı değiştirilmiş organizmalar organik hayvansal üretimde girdi olarak kullanılamaz. Gen teknolojisi metotları ile hayvan ıslahına izin verilmez. Büyüme veya üretimi artırıcı maddelerin kullanımı ve üremeyi kontrol etmek amacıyla veya diğer amaçlarla hormon ya da benzeri maddelerin kullanımı yasaktır. Ancak hormonlar, tedavi amaçlı veteriner hekim uygulaması olarak hasta hayvana verilebilir.

d. Veteriner tıbbi ürünleri kullanıldığında; konulan teşhis, müdahale yöntemi, ilacın dozu, ilacın etken maddesi, tedavi süresi ve ilacın kalıntı arınma süresi ile birlikte kullanılan ürün kayıt edilir.

e. Bir hayvana normal koşullarda verilen veteriner tıbbi ürünlerinin son uygulandığı tarih ile bu hayvanlardan organik ürün elde edilme tarihi arasındaki süre, organik yetiştiricilikte, konvansiyonel yetiştiricilikteki uygulamanın iki katı veya kalıntı arınma süresi belirtilmemiş hallerde ise 48 saattir.

f. Aşı uygulamaları, parazit tedavisi veya ülkemizce zorunlu olarak belirlenen hayvan hastalık ve zararlıları ile mücadele programları haricinde, bir hayvana veya hayvan grubuna bir yıl içerisinde üçten fazla kimyasal sentezlenmiş veteriner tıbbi ürünler veya antibiyotiklerin uygulanması halinde ya da üretken olduğu yaşam süresi bir yıldan az olan hayvanlarda bir defadan çok muamele gördüyse, söz konusu hayvanlar veya bu hayvanlardan elde edilen ürünler organik ürün olarak satılamaz ve yeniden geçiş sürecine alınır. Buna ait kayıtlar müteşebbis tarafından tutulur.

ANNEX 5, SECTİON 3

MİNERAL DERİVED FEED

Sodium (refined sea salt, sodium carbonate, calcium carbonate, calcium lactate, calcium glyconate), potassium (potassium chloride), calcium, phosphorus, magnesium (magnesium ozide, magnesium sulphate, magnesium chloride, magnesium carbobnate), sulphur (sodium sulphate)

ANNEX 6, SECTİON 1.1

NUTRİTİONAL SUPPORT

Vitamins

Trace elements

Iron, Iodine, Cobalt, Cupper, Mangane, Zinc, Molibden, Selenium

U.S. Herbal Organizations Specifications and Monographs

American Herbal Pharmacopoeia®

The Mission of the AHP is to promote the responsible use of herbal medicines and insure they are used with the highest degree of safety and efficacy as is achievable.

Our primary way to accomplish this is through the development of standards of identity, purity, and analysis for botanicals, as well as to critically review traditional and scientific data regarding their efficacy and safety.

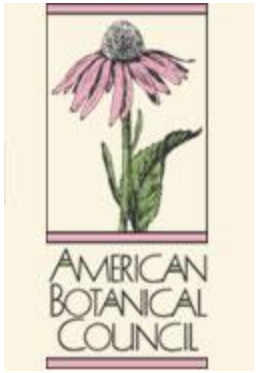
…independent quality control requirements for producing herbal products need to be established to ensure that the highest degree of safety and effectiveness is achieved.

While herbal medicines are well integrated into the health care systems of many other nations, this is not the case in the U.S. Authoritative information regarding proper use and manufacture of herbal medicines is lacking.

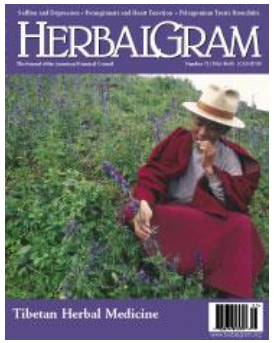
AHP will disseminate these works through…monographs…including Western herbs most frequently used in the United States.

…ensuring herb identification and quality are the foundations of the herbal products industry.

Herbal Material Identification: *References*… Herbal Pharmacopoeia, Monographs, USP…establishing a reference program, key identifying factors



David Pasco, PhD proposed that the approach to standardizing botanical products by measuring bioactivity can be done in the same way as conventional pharmaceutical products such as insulin or cytokines. Examples given that demonstrated the usefulness of this approach included…Aloe polysaccharides from *Aloe vera*.



Herbal Gram Issue 71: *Improving the Quality of Reporting Randomized Controlled Trials Evaluating Herbal Interventions: Implementing the CONSORT Statement*

"Given that herbal medicinal products are widely used, vary greatly in content and quality, and are actively tested in randomized controlled trials (they) must clearly report the specifics of the intervention.

Mark Blumenthal…"that's a great clinical study, but what the (heck) were they testing?"