Asia Aromatherapy: A New Way to Explore the Activity Spectrum of Essential Oils

Kurt Schnaubelt, Pacific Institute of Aromatherapy, San Rafael, Ca 94903, USA

1) Introduction

In the current scientific discourse the physiological effects of essential oils are considered to be caused by specific molecules, respectively specific molecular structures. For example the current regulatory discussion in the European Union about the sensitizing potential of natural extracts is conducted within this paradigm. The salient example is Lavender oil and its two main components linalool and linalyl acetate. The latter two were for instance tested with the currently accepted model 'Local Lymph Node Assay' for their sensitizing potential (**1**). The conclusions about the physiological properties were the applied to the whole oil.

Within this paradigm it is further assumed that synthetically prepared substances have identical physiological properties as the components of natural origin, if they can be represented by an identical structural formula.

This issue has been discussed (**2**) and it is apparent that the assumption of identical physiological activity of synthetic and natural substances, on the basis of a common structural formula, ignores some obvious differences between the two. Natural products usually have different enantiomeric ratios and also different isotope abundance. The postulated purity of synthetics is also a chimaera. The physiological effects of synthetic linalool are modified by whatever impurities are present. It is clear that impurities arising from laboratory synthesis will be different from those arising through enzymatic synthesis in the plant. In fact, the so-called impurities arising in the plant are by definition physiological as they arise in a living organism. Those from laboratory synthesis, with its much more extreme reaction conditions and reactants are NOT. Not only are natural or enzymatically synthesized substances different from their lab synthesized counterparts (isotope abundance) they also occur within a different set of byproducts.

These issues are of major relevance to the recognition of the physiological properties of complex plant extracts, essential oils, CO_2 or solvent extracts alike. In fact there is a rather glaring dissonance between orthodox viewpoints, advanced in the European regulatory discussion allegedly intended to ensure the absence of hazards in natural substances and the aromatherapy community which uses the substances maligned by the European bureaucracy as effective healing agents.

A resolution of these issues lies in broadening the scope from a 'chemistry only' perspective to include well established concepts from the discipline of biology, the science of life.

2) The Biological Framework of Aromatherapy

Evolution, Signaling, Pleiotropic, Emergent Properties, Organicism

2.1) The Evolution of Secondary Plant Metabolites

Million years ago	Eon	Secondary Metabolites
22	Grasses	expand from the Asian plains
141	Angiosperm insect co-evolution	Sesquiterpene lactones
233	Conifers develop rapidly	
281	Gymnosperms dominant	Terpenoids in atmosphere
323	Swamp forests	
391	Horsetails, Lycopodiae, Gymnosperms	
433	Vascular plants	Phenyl propanoids form lignin
462	Primitive landplants	
535	Algae and seaweeds	Fast expansion of life in tropical oceans
542 - 0	***Phanerozoic***	
2500 - 1900	Eukaryotes arise	
2500 - 542	***Proterozoic***	
3300 - 3000	Archaea and bacteria	Photosynthesis and subsequent synthesis of amino acids, carbohydrates and steroid triterpenes
3800 - 2500	***Archaean***	
4600 - 3800	***Hadean***	Chemical evolution

Table 1: Earth Ages

The first and foremost quality which makes natural substances hugely different from novel synthetics is that they arose through billions of years of evolution. Adopting the current Big Bang model of the origin of everything we can look at an evolution timeline of molecules we find in plants in particular and in animate nature in general.

About 500 million years ago life moved from the oceans on to land. The first evolving primitive plants settling in the moist environment of the ocean shores must have been in intense competition with other organisms in water and on land. While it is impossible to know exactly with which organisms the very first plants were in competition, it is clear that viruses, bacteria and fungi (or yeasts) predate plants.

If plants could make substances which would defend against challenges by these microorganisms, they would clearly enjoy an advantage in their quest for survival and reproduction.

Angiosperm plants make their first appearances approximately 100 mio years ago. Co-evolution with insects proved to be a most successful strategy. In their rapid evolution, angiosperms refined the already existing strategy of making molecules which achieve effects by interacting with molecular targets in other organisms.

Understanding the origin of the physiological activity of essential oils (and more generally complex natural extracts) is tantamount to a more inclusive understanding of their physiological qualities and therapeutic potential. Evolutionary processes are at the very beginning of plants developing highly active secondary metabolites.

How Did Plant Substances Acquire Physiological Activity

Plants, like all multicellular organism, are made up, on the cellular level of organization, by so-called eukaryotic cells. In other words, plants, animals and humans are all made up from the same type of cell. The precursors to eukaryotic cells are so-called prokaryotic cells, archetypical single cell organisms. Many of todays pathogenic bacteria are in fact prokaryotic single cell organisms.

These very first life forms, prokaryotic cells, had at their disposal all the basic biosynthetic pathways which produce the molecules of life such as carbohydrates, proteins, fats and DNA and RNA (see Table 1). As life evolved into the more complex eukaryotic cells and then into multi cell organisms it was, and still is, employing the same set of biosynthetic pathways generating the basic molecules of life. And as all life goes back to the same cellular and ultimately molecular ancestors, even many of the enzymes and functional proteins which regulate the synthesis of the molecules of life are very similar or even identical in plants, animals and humans. Of course there are also differences, animals have not preserved the capacity to photosynthesize!

In general terms, this similarity of the biosynthetic and cellular architecture of plants and mammals, including humans, is the main reason why plants can produce substances or messengers that are immediately understood by the mammalian and human organism, as they speak the same chemical and enzymatic language. In other words plants produce messenger molecules readily interacting with molecular targets in the mammalian/human organism.

A typical example for this phenomenon are the effects and influences exercised by essential oils on HMG CoA Reductase and thereby cholesterol synthesis and the formation of new tissue (for detail and references see **3**).

Another well recognized example is the efficacy of plant extracts against microbial, fungal or viral pathogens. This ability arose as plants, with secondary metabolites that helped defend against challenges by micro organisms, enjoyed selective advantages and reproduced more efficiently. The ability of plants to produce an ever widening spectrum of secondary metabolites arising as by-products of the main biosynthetic pathways is one of the less recognized but intensely fascinating aspects of gymnosperm and especially angiosperm evolution.

Cholesterol synthesis shall again serve as an example. Cholesterol is an important molecule of life, a primary metabolite. It provides necessary rigidity and stability to the cell membrane. It is essential for formation and regeneration of tissue. The synthesis of cholesterol proceeds through various stages, one of which is the synthesis of terpenoids from two molecules of isoprene.

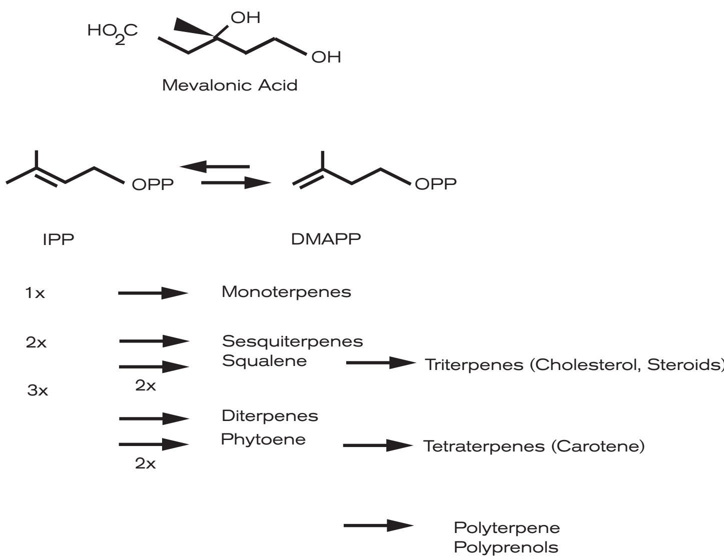

Figure 1: Terpene Synthesis

By sidetracking low molecular substances like terpenoids from the main biosynthetic pathway and modifying these low molecular components by more or less specific enzymes into ever new variations, intense molecular modeling and evolution of ever more complex secondary metabolites ensued.

As an immediate consequence of their lipophilic nature, terpenes, sesquiterpenes and also phenylpropanoids (see further down), have the ability to disrupt the membrane of challenging microorganisms or viruses (for references see **3**).

As the lipophilic products also potentially disrupt membranes of the plant cell, the trial and error of evolution often led plants to sequester the synthesis and/or storage of these defensive substances into specialized cells, so the plant is not damaged by its own product.

To sum up: terpenes and sesquiterpenes are lipophilic intermediates of the cholesterol synthesis. Over time, plants have learned to sidetrack some of these and to sequester them into special cells or spaces thereby effectively improving the plants survival odds.

Similarily, the phenyl propanoids encountered in many medicinal and aromatic plants (MAP) are byproducts of the amino acid metabolism. Amino acid synthesis is tied to photosynthesis, it takes place in the chloroplast. As the amino acid phenyl alanine undergoes a series of modifications to ultimately form macro molecules which constitute lignin, the wood of the plant, low molecular intermediates are spun off to turn into one of the many phenyl propanoids such as eugenol or methyl chavicole that have such extremely wide ranging defensive, turned therapeutic, qualities.

2.2 Signaling

As all multicellular life is based on the chemical and synthetic processes available to eucaryotes, it is not surprising that a chemical language has evolved of which large parts are understood by all forms of life. In other words many different organisms have molecular targets which respond (interact) in one way or another with secondary plant metabolites.

In the past, research in this area was mainly limited to identify the influence of secondary metabolites on Phase I enzymes as the cause of undesirable “drug interactions.” Only recently have the cellular processes triggered by secondary metabolites become an object of research looking for potential therapeutic effects.

This current research suggests that the interactions between natural extracts and the multitude of molecular targets in the cell may reach a degree of complexity that conventional reductionist experimentation can only inadequately describe. While basic properties of the main components in plant extracts can often be readily demonstrated, there are also many phenomena of therapeutic activity associated with plant extracts that cannot be described let alone measured by conventional pharmacology.

This contention is indirectly supported in the recent publication “Molecular Targets and Therapeutic Uses of Spices: Modern Uses for Ancient Medicine” by Aggarwal and Kunnumakkara **(4)**. On the one hand there is Turmeric and the many physiological effects that could be shown for its characteristic component curcumin, conforming to the conventional perspective of attributing activity to the active ingredient. On the other hand there is a review on therapeutic effects of Cardamom. An impressive list of publications attests to its physiological and therapeutic activity. However, for lack of a substance characteristic to Cardamom, the ubiquitous 1,8 cineole is declared the active ingredient and credited with causing Cardamom’s physiological activity. Following this logic the wide spectrum of essential oils with a high cineole content should have the same or similar activity as Cardamom. This latter contention is probably true, but difficult to express in conventional terms.

Another well known example for the difficulties in connecting physiological activity to single (or a small number of) active ingredients is presented by the many valuable properties encountered in Frankincense essential oil **(5,6,7)**. Experience in the aromatherapy community, and probably also by TCM users suggests that Frankincense oils have many valuable properties almost independent of geographical or botanical origin and the apparently very varied composition these oils have **(48)**.

For forward looking aromatherapy it is crucial to find a theoretical model which is better suited to describe observable physiological activity of essential oils (and other complex natural mixtures). Such relevant concepts are summarized by the term 'systems biology,' emergent properties, organicism and pleiotropic effects **(3)**. In this paper it will be argued that 'systems biology' is congruent with the observations made in the reality of aromatherapy applications.

Within the systems biology perspective it seems logical to derive valuable clues for the true value of the MAPs and spices not only from scientific experimentation but also from the fascinating cultural and commercial history that has made these plants an integral part of human life for millennia **(8, 9)**. In the true spirit of science as unbiased inquiry the historical and cultural aspects of spices and the way they found their way across planet earth should be examined for information about healing qualities that may have been forgotten. It is not known what sequence of evolutionary triggers caused Ginger to generate gingerols and Turmeric to synthesize curcumin. But we do know that for as long as there has been some form of historical narrative, humans who knew those plants also used them to benefit from them. We also know that humans were instrumental in the radiation of these plants either through simply bringing them along on their migrations (Ginger, in the Austronesian migration) or through trade, as in the case of Frankincense and Myrrh.

Relegating all knowledge of prior generations to the dustbin of superstition, ostensibly for lack of scientific evidence, does not seem to be a truly scientific approach to the healing properties of aromatic plant extracts. Instead it seems to be the intentional advocation of one method over another, based on the influence of current economic models.

2.3 Pleiotropic Effects

In the past medical and pharmacological research into plants has focused exclusively on substances with selective activity, congruent with the unspoken assumptions that specific molecular structures are needed to counteract (treat) specific symptoms (of disease). However, this assumption often does not correspond to what is observed in real life, because it does not account for the effects of the much larger number of plant components which have multiple, non-selective effects.

Recent research demonstrates that even the simplest molecules from the most ubiquitous and common plants find numerous molecular targets in our organisms often inducing desirable effects. One molecule of the plant world often has many different physiological effects within one organism. This quality of displaying multiple physiological effects is called pleiotropic (Webster: producing more than one effect). For example it is entirely possible that an essential oil not only is effective against a specific virus, but at the same time against a whole range of pathogenic bacteria while also being anti-inflammative by inhibiting arachidonic acid metabolism.

Hence the long lists of diverse indications that many traditional medicinal works attribute to a single plant species. This diversity of indications is increasingly supported by current science. Cardamom for instance is described in Tang dynasty texts as effective for strengthening the mind, increase the breath, stabilize the soul and to relieve bronchial and lung conditions **(10)**. According to contemporary research Cardamom has gastroprotective, hepatoprotective, cardiovascular, anti-inflammative, analgesic, anti-oxidant and anti carcinogenic effects **(4)**.

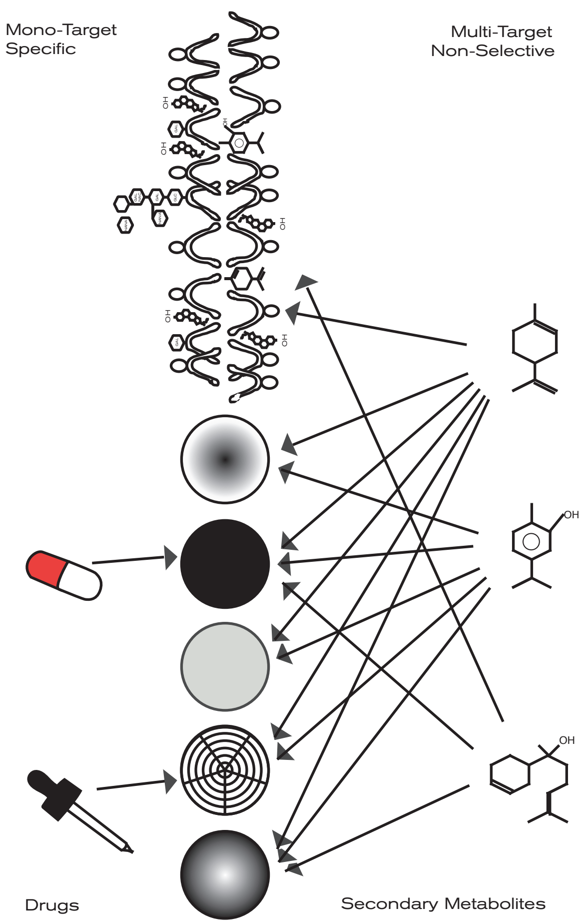

Figure 2: Pleiotropic Effects of Secondary Metabolites vs. Selective Effects of Conventional Drugs

Recognizing the pleiotropic nature of many essential oil components is also new to the aromatherapy field itself. For the longest time the aromatherapy authors have taken their cues from conventional medicine when it came to describing the medicinal effects of essential oils. This is understandable, given the history of discovery of physiological activity of essential oils. From Gattefossé to Valnet **(11,12)** and later authors the molecular structures of their main components were credited as the origin of their therapeutic properties.

2.4 Systems Biology and Biological Levels of Organization

Recognizing the pleiotropic effects of essential oil components is followed by the realization that in many essential oils there are not only one or two components present which exhibit pleiotropic effects. Instead many essential oils have over a hundred of easily identifiable components. And even this larger number seems arbitrary as the number of components identified in an essential oil often is a function of the sensitivity of the analytical process. When trace components are included in the count the number of substances present in an essential oil can be significantly higher.

Following evolutionary reasoning it is unlikely that only those substances that already have been investigated display pleiotropic effects. It is reasonable to assume that many components not yet investigated have the same pleiotropic nature.

As a result, the number of physiological reactions caused by the many different components of an essential oil can be significant. While many different components may interact with identical targets it is still obvious that the interaction of complex natural extracts with many molecular targets at the same time represents a process, which is only inadequately described measuring the activity of the so-called active ingredient in one or two pharmacological models. The degree of complexity reached by the healing interaction of essential oils with human physiology is such that theoretical approaches such as organicism, transcending reductionist pharmacology, are sorely needed.

2.5) Emergent Properties

Systems Biology respectively organicism state, that on each level of organization of living organisms properties emerge which cannot be predicted, even from the most intimate knowledge of the detail of the lower level of organization **(13)**. In the context of the therapeutic properties of essential oils this means that the whole, authentic oil or extract indeed presents effects that arise at the level of the whole plant organism, which may not be obvious from knowing the molecular make up of the oil.

Example: As plants address the challenges presented by their environment they will express a subset of secondary metabolites from their genetical reservoir, which is best suited to ensure further survival and propagation under the specific conditions **(14)**. This is why essential oil composition may vary slightly or substantially from harvest to harvest. This is also why in aromatherapy authentic oils where these fluctuations are not standardized away are preferred, because the precise composition of such oils represent the struggle of the plant for survival and the inherent benefits (emerging at the level of the whole plant) **(15)**.

The framework of organicism and emergent properties provides a rational explanation for the phenomenon that in aromatherapy healing effects are experienced by essential oil users, which cannot be reproduced or understood by orthodox pharmacology focusing on isolated molecules.

Example: Resistance to Pathogens

It is well known that bacterial pathogens develop resistance to conventional antibiotics, often in the course of only a few years. This is a consequence of the narrow focus of antibiotics. They are generally highly selective inhibiting a single mechanism in the formation or metabolism of a pathogen. When one microorganism has changed just enough to survive the antibiotic, it will replicate freely.

Essential oil components are fundamentally different. Their pleiotropic activity makes it practically impossible for microorganisms to develop resistance. Microorganisms may be able to resist the attack on one of their targets, but this leaves all the other targets of the essential oil still vulnerable.

In addition some targets are so central and important to the existence of the microorganism that it cannot simply abandon those targets by a slight mutation. There is no way in which a microorganism can counteract an attack on its membrane by lipophilic essential oils. The microorganism simply needs its membrane!

Variation

As plants change with the seasons so does their production of defense secondary metabolites. The composition of an essential oil changes continuously during the life cycle of a plant. It varies between different organs of the plant and also between individuals of a population. This constant change is reflected in the composition of truly authentic essential oils. Different from standardized essential oils required for industrial production processes, authentic essential oils reflect the seasonal and climatic variation of nature, changing from year to year or from harvest to harvest.

This constant variation has strong ecological advantages. Experience has shown that the development of resistance is inherent to single component drugs with specific single modes of action (antibiotics)!

Example: The Pleiotropic Effects of Limonene

Above we argued that biological evolution, for the most part, did not produce metabolites with very specific activity but rather components with pleiotropic activity, which could interact with multiple physiological systems.

This contention shall be illustrated with the example of the limonene molecule, a major constituent of many citrus and other oils. Limonene induces a number of apparently unrelated physiological activities. Yet the different properties of limonene only appear unrelated, because of cultural and economic bias to seek cures for cancer separate from those for heart disease and also separate from limonene's influence on liver enzymes **(3)**.

Removing Carcinogens

Limonene slightly inhibits Phase I liver detoxification enzymes simultaneously inducing Phase II enzymes. The net result is that the production of potentially toxic or even carcinogenic intermediates, which sometimes occurs in the Phase I process, is slowed and the accelerated Phase II process removes them instantly. Under the influence of limonene potential carcinogens cannot linger.

Inhibiting Tumor Growth

The limonene molecule selectively inhibits reproduction of tumor cells via the inhibition of HMG CoA Reductase.

Inhibiting Herpes Virus

Limonene also is a highly active agent in the treatment of herpes lesions.

Complexity

These three effects - and most likely many additional ones - occur concurrently whenever the organism is exposed to limonene, illustrating how complexity arises, ultimately giving natural plant extracts their unrivaled spectrum of activity.

In the past, the comparatively rare secondary metabolites displaying selective activity, received most of the scientific attention for obvious reasons. But there are many more secondary metabolites, not with a narrow selective, but a very broad pleiotropic spectrum of physiological activity.

The pleiotropic or non-selective effects of essential oils arise through biological evolution. They evolved on a time scale much larger than that of even multiple generations. The plant - human interactions, as they unfold before us, have existed for ever. Cinnamon and Clove were as beneficial to humans in Hildegard von Bingen's time as they are today. This suggests a reexamination of our cherished western notion of progress, that better conditions or medicines arise (only) as a result of human activity.

In the following paragraphs we shall discuss some of the most common therapeutic properties of essential oils and their components as they are recognized by conventional methods. After that essential oil qualities which are recognized within aromatherapy or as potential therapeutic agents by cellular biology, will be identified as such and described. The focus will be on aromatic plants of Asian origin.

Table 2: Commonly available Essential Oils and Extracts of Asian Origin used in Aromatherapy

Most Familiar Essential Oils of Asian Origin

Basil Vietnam, Ocimum basilicum
Benzoin resinoide, Styrax tongkinensis
Black Pepper, Piper nigrum
Cajeput, Melaleuca leucadendron
Camphor tree, Cinnamomum camphora
Cardamom, Elletaria cardamom
Cassia, Cinnamomum cassia
Cinnamon, Cinnamomum verum
Citronella, Cymbopogon nardus
Clove, Eugenia caryophyllata
Combava, Citrus hystrix
Cypriol (Nagarmotha), Cyperus rotundus
Dill, Anethum sowa
Fenugreek, Trigonella foenum-graecum
Frankincense, Boswellia carterii
Geranium China, Pelargonium asperum China
Ginger, Zingiber officinale
Ho Wood, Cinnamomum camphora, linalool
Lemon, Citrus limon
Lemongrass, Cymbopogon flexuosus
Massoia, Cryptocaria massoia
May Chang, Litsea citrata
Myrrh, Commifora molmol
Niaouli, Melaleuca quinquenervia
Nutmeg, Myristica fragrans
Palmarosa, Cymbopogon martinii
Gingergrass, Cymbopogon martinii var. Sofia
Patchouli, Pogostemum cablin
Persian Lime, Citrus latifolia
Ravintsara, C. camphora type cineol
Siam Wood, Fokienia hodginsii
Spikenard, Nardostacys jatamansii
Star Anise, Illicium verum
Vetiver, Vetivera zizanoides
Wintergreen, Gaultheria procumbens
Ylang Ylang, Cananga odorata
Yuzu, Citrus junos

Extracts from Rhizomes and Resins

Calamus, Acorus calamus
Costus Root, Aucklandra costus
Elemi, Canrium luzonicum
Frankincense (B. carterii)
Frankincense (B. serrata)
Galbanum, Ferula galbaniflua
Galgant, Alpinia galanga, A. officinarum
Ginger, Zingiber officinale
Guggul, Commiphora mukul
Myrrh, Comiphora molmol
Styrax, Liquidambar orientalis
Thai Ginger, Zingiber cassumunar
Turmeric, Curcuma longa
Turmeric, Curcuma xanthorrhiza

Precious Fragrance

Agarwood, Aquilaria agallocha
Ambrette Seed, Abelmoschus moschatus
Araucaria, Neocallitropsis pancheri
Himalaya Cedar, Cedrus deodora
Lotus blue, Nymphea cerulea
Lotus white, Nelumbo nocifera
Osmanthus, Osmanthus fragrans
Sandalwood, Santalum album

3) Selected Properties and Applications: Conventional

Following are some important examples of therapeutic or curative effects of essential oils recognized by conventional pharmacology. This body of knowledge about therapeutic effects of essential oils was compiled even before there was widespread awareness about the nature of plant secondary metabolites.

Antibacterial Activity

Essential oil efficacy against many bacterial pathogens has been demonstrated in countless experiments, starting as far back as 1880. These studies suggest that essential oils either inhibit bacterial growth or kill bacteria outright. Possibly the most comprehensive studies were performed by Paul Belaiche in the **1970s (16)**.

While antibacterial efficacy was clearly demonstrated, its mechanism was harder to elucidate. Unlike antibiotics, which are active due to inhibiting an identifiable single target, the activity of essential oils, impairing a bacterium in multiple physiological systems as well as in membrane functionality, is only now understood.

A specific benefit of the unique biological qualities of essential oils is their capacity to treat also those infections caused by antibiotic resistant bacteria (MRSA) **(17)**.

Antifungal Activity

Studies by Maruzella in the 1960s **(18)** and by Pellecuer in the 1970s **(19)** demonstrated essential oil efficacy against fungi and yeasts in vitro, but again, no mechanisms have been derived from these experiments. It was shown in the 1990s that the sterol insensitive key enzyme HMG CoA Reductase in fungi is inhibited by essential oils **(49)**.

Antiviral Activity

A fundamental study by Lembke and Deininger published in 1987 **(20)** demonstrated for the first time the superior antiviral activity of a broad spectrum of essential oil components. Many more studies follow worldwide, corroborating its findings. Efficacy of many oils and their components against a wide range of viruses has also been demonstrated in vitro and occasionally in clinical trials. Different cellular mechanism for the observations have been proposed **(51)**.

Effects Mediated Via The Autonomic Nervous System

Ground breaking studies have been published by H. Wagner in **1973 (21)**. Spasmolytic and sedative effects of essential oils were shown in different pharmacological models. The ability of essential oils to ease anxiety, heart palpitations, nervousness and heat flashes has been confirmed in double blind studies in the 1970s **(22)**.

Anti-inflammative Activity

Classic studies by H. Wagner and O. Issac have been published in the 1970s **(23)**. Many sesquiterpene hydrocarbon components of essential oils have been demonstrated to have anti-inflammative effects on tissue. Cellular or biochemical mechanisms have become much clearer in the recent past, by understanding the diverse events connected to inflammation. In addition many sesquiterpene hydrocarbons have a capacity to dissipate free radicals. Components in Helichrysum italicum have been shown to mediate their tissue protective and regenerative quality by effectively scavenging free radicals **(24)**.

Osteoporosis

Studies by Muhlbauer, Lozano, Palacio, Reinli and Felix establish common essential oils as unexpected and effective agents to prevent osteoporosis **(25)**.

Progesterone Estrogen Balance

Vitex agnus castus has been shown to be a singularly effective agent to re-equilibrate progesterone and estrogen levels and to have pronounced benefits for PMS and menopausal complaints. While the effect is clearly established, no specific component has so far bee identified as causing it **(26)**.

Summary

In the middle of the 20th century essential oil pharmacology saw an accumulation of data with an emphasis on antimicrobial activity and acute conditions.

4) Selected Properties and Applications: Current Perspectives

With the growing popularity and spread of cellular and molecular biological methods also came a resurgence of research into the physiological effects of many traditionally valued spices and their characteristic components. This research has concentrated on the molecular biology of chronic metabolic diseases such as diabetes or arthritis as well as carcinogenesis.

For aromatherapy this is an encouraging addition. Due to the lay character of aromatherapy the conditions that have been explored by the aromatherapy community were always of a more acute nature, as the outcome of a treatment is more easily determined with conditions involving shorter time frames.

If the conventional effects of essential oils described in the above paragraphs can be generally attributed to the presence of specific chemical components the effects described in the following paragraphs can be more readily understood as a result of evolutionary processes of plants surviving in their environment.

Inflammation

A wide range of components from essential oils have been shown to be effective in inhibiting arachidonic acid metabolism, Cyclo oxygenase 2 or Lipoxygenase and hence inhibit or treat inflammation and chronic conditions.

Arthritis

Many of the resins and rhizomes of Asian origin have direct influence on the above listed molecular targets and are effective in easing the symptoms of arthritis and arthrosis.

Diabetes

Components of spent Cinnamon (after distillation of Cinnamon bark essential oil) have been shown to effectively ease diabetes conditions. Fenugreek, Garlic, Ginger, red Chilies and Rosemary have also been traditionally used to minimize the effects of diabetes.

Hepatitis B and C

Long term clinical studies by Giraud-Robert have shown that various oils are effective in the treatment of Hepatitis B and C, but no mechanisms are proposed at this point **(27)**.

Liver Detoxification Enzymes

Essential oils are among the native agents responsible for the development of the liver detoxification enzymes. Coexisting and co-evolving with the plant world and its secondary metabolites triggered the development of the enzymes that now are part and parcel of human metabolic make-up. The fact that the human organism has these enzymes in place which have specifically evolved to remove essential oils, formerly perceived as xenobiotics, explains why real toxicity among essential oil components is observed only in very few and easily identifiable instances.

All this suggests that interacting with plants or plant products is vital to the healthy functioning of our metabolism. It also suggests that living on a diet of industrial foods, which were not part of the diet of our ancestors may lead to accumulation of toxins, as we do not have the necessary enzymes to remove the foreign non-nutrients inherent in such a diet.

Secondary Metabolites Trigger Detoxification Enzymes

One of the most overlooked healing properties of essential oils is their ability to induce or to inhibit Phase I and Phase II liver detoxification enzymes. (For detail and references see **3**). This results in a specific ability of essential oils to induce overall detoxification. Whenever essential oils are used, internally or topically, the removal of metabolic waste is stimulated. In modern aromatherapy this effect is intensely utilized, for instance to reduce side effects of conventional cancer treatments.

Molecular Targets Relevant to Carcinogenesis, Angiogenesis, Metastasis and Chronic Inflammation

The work of Bharat Aggarwal and others shows that many components, especially from Asian origin spices have anticancer effects in diverse models. Components such as curcumin from Turmeric or 6-gingerol from Ginger have a broad range of effects on growth factors, **NF kB** and apoptosis among many other targets, which all act against carcinogenesis or tumor development and metastasis and are hence promising candidates for further study of their preventive and curative potential with respect to cancer.

While Aggarwal and other researchers working in this direction focus on the properties of characteristic components of single spices such as piperin or curcumin there is also solid evidence that a wide array of terpenes have significant antitumor properties.

Research in the 1990s, focused on the antitumor activity of terpenoid essential oil components. Perillyl alcohol was tested in clinical trials for its efficacy against mammary cancer. A key patent claiming cancer treatments with terpenoids is in the possession of the United States. PIA conducted a symposium “Essential Oils and Cancer” in the year 2000, where Charles Elson and Dennis Peffley, two of the most important contributors to the NIH sponsored research, presented their results **(49)**. They found that many mono and sesquiterpene components had varying degrees of antitumer activity. Their research identified a different of mechanisms contributing to the effect.

Taking into account past and recent research on on antitumor proeprties of terpenoids it is not unreasonable to surmise that essential oil might in fact have significant promise in chemoprevention and also treatment of cancer. (For reference to a significant clinical study see further down, 6) Essential Oils for Cancer).

5) Essential Oils for Cancer

Ameliorating the Side Effects of Conventional Cancer Treatments

While the in vitro data about many spice extracts are very encouraging maybe the single most important contribution to a better utilization of essential oils in the treatment of these serious diseases has come in the form of the clinical research of Anne-Marie Giraud-Robert.

As is well known, conventional cancer treatments with chemo or radiation therapy produce often the most debilitating side effects such as chemotherapy induced vomiting and nausea (CINV). These side effects are often of such intensity that the patients forgo treatment. In her study, including, lung, pancreas, breast, uterine cancer as well as melanoma patients, Dr. Giraud-Robert has shown that concurrent treatment with essential oils reduced side effects of the conventional drugs and improved patient quality of life and significantly **(50)**.

More than 1800 cancer patients, who received allopathic treatment concurrently with essential oil treatment, had significantly higher survival rates than patients with comparative cancers and allopathic treatment alone. These observations were true for all types of cancer that were observed.

Dr. Giraud-Robert uses essential oils principally to reduce the side effects of conventional treatments. It can be argued that reducing the side effects of the conventional treatment allows patients to better tolerate those treatments, which ultimately leads to better outcomes. Following is a brief description of the most important oils used to ameliorate the side effects of conventional cancer treatments.

Ravintsara (Cinnamomum camphora)

Ravintsara reduces physical and mental asthenia, which in turn helps the patient make decisions and regain self-confidence. During treatment, it counteracts depression. Ravintsara is sedating, promotes sleep and improves sleep quality; it reduces anxiety. Its antiviral activity and general improvement of immune response significantly reduce the risk of infection during chemotherapy. Ravintsara reduces most side effects of Interferon treatment such as depression, insomnia, muscle pains and fatigue. It reduces joint pains and stiffness caused by antiaromatase-type anti-hormonal treatment for breast cancer. At the end of classical treatment, it stimulates the patient's immune system.

Greenland Moss (Ledum groenlandicum)

Greenland Moss is very effective for lessening nausea and vomiting during chemotherapy; it reduces transaminases and gamma-GTs levels when those are pathologically elevated. It apparently acts as an antitumor agent by inducing cellular apoptosis. After conventional treatments, it is effective for draining toxins from the liver and kidneys.

Everlast (Helichrysum italicum)

Helichrysum essential oil is extremely useful after surgery for reducing hematomas, to improve healing, prevent cheloid scars, reduce lymphatic edemas following ganglionic curage and to prevent fibrous bands in abdominal surgeries. Helichrysum is most useful in breast reconstruction, for its anti-inflammative, painkilling and anti-edematous effect and to eliminate old, hardened hematomas. Psychologically speaking, it soothes the soul's "bruises" and helps with emotional shocks.

Niaouli (Melaleuca quinquenervia, cineole type)

Massages with oils containing Niaouli, reduce lymphatic edemas. Niaouli stimulates the immune response. It prevents radio epidermatitis during radiation therapy. It reduces the breast reconstruction period. Niaouli has powerful anti-infectious, antibacterial, antiviral and antimycotic properties.

Myrrh (Commiphora molmol)

Myrrh is equally valuable during and after conventional treatment. It drains toxins from the kidneys during and after chemotherapy. Myrrh stimulates the nervous system and has anti-depressant properties. It has strong analgesic properties. Myrrh has a very profound effect on a person's entire being by reequilibrating the psycho-neuroendocrino - immunological systems. Myrrh induces cellular apoptosis **(3, 50)**.

6) Rhizomes and Resins

To further explore the accumulating evidence of antitumor effects, especially in extracts of Asian rhizomes and resins, some of the properties of Ginger and Frankincense will be highlighted. These two plants are selected, because they illustrate very well the stunning diversity of physiological properties that can be vested in the extract of a single plant species and the attention that needs to be paid to the pleiotropic character of many essential oils and aromatic extracts.

Ginger

As early as 4000 B.C.E. Ginger spread with the last big human migration - the Austronesian migration - all across Southern Asia and the Pacific in the east and Madagascar in the west. Ginger was maybe the first success in globalization. The traditional healing systems of the East, especially Ayurveda, cannot be imagined without Ginger. By now indigenous people in the rest of the world have recognized the healing powers of Ginger and sciane is gradually following suit.

A look at the research directed towards the pharmacological properties Ginger quickly confirms its diverse physiological activity. The properties of Ginger's lipophilic (essential oil components) and more polar components (only present in CO_2 extracts) have been given quite some attention. In pharmacological terms Ginger's anti-inflammatory/anti-rheumatic properties seem to be most easily verified. But beyond that Ginger appears to contribute to human health in many different ways.

From an evolutionary perspective this is not surprising. It makes sense that a plant that relies on human activity for its propagation got to this point by offering valuable qualities to the other organism. Ginger is connected to recent human history in ways few plants are. In his excellent book "Dangerous Tastes" Richard Dalby discusses the universe of spices past and present. He starts his long list of aromatics with none other than Ginger **(9)**.

In the context of aromatherapy there are generally two principle ways in which Ginger oil is used, as the classic steam distilled essential oil and also as a CO_2 extract which typically contains not only the expected low molecular terpenoids, but also the pungent gingerol and shogaol components, which are not found in the steam distilled oil.

These pungent components of Ginger were tested in 1986 to study their effects on inflammative processes. It turned out that these components were powerful inhibitors of the processes that lead to inflammation. Ginger is a potent prostaglandin and thromboxane inhibitor. It is thought that increased Thromboxane levels are instrumental in anxiety, depression and psoriasis.

Ginger also has an anti-vomiting activity and an effect on gastrointestinal motility. It protects the lining of the stomach against aggressive agents such as ethanol, hydrochloric acid and lye. Zingiberene and gingerol inhibit gastric lesions.

In human tests it was found that Ginger inhibits Thromboxane TXB_2 and has anti-motion sickness activity. Ginger has also been reported repeatedly to have most beneficial effects for patients suffering from arthritis and migraines.

By now there is a substantial body of literature on the benefits of Ginger. For most of the 20th century Ginger and its extracts were more or less ignored by official science until the tide shifted in the mid 1980s **(28,29,30).** It is probably fair to say that the basic assumptions of traditional systems about the wide ranging properties of Ginger root are based in a reality which is now also discovered by scientific experimentation.

Aromatherapy: Given Ginger's composition of sesquiterpenoids and pungent components which also originate from the terpene biosynthesis it is not surprising that most of Ginger's activities are on the level of ying qi, they address metabolic processes. Following are some selected references to just a few the rising number of studies on the properties of Ginger.

Effect on Colon Cancer

A study suggests that ginger extract may bring to bear its antitumor effects on colon cancer cells by suppressing its growth, striking the G0/G1-phase, reducing DNA synthesis and inducing apoptosis **(31)**.

Effect on Lipid & Glucose Concentration in Blood

A methanolic extract of dried rhizomes of ginger produced a significant reduction in fructose-induced elevation of lipid levels **(32)**.

Antioxidant Action

The antioxidant properties of [6]-gingerol make it an effective agent to contain ultra violet B (UVB)-induced reactive oxygen species production and resulting COX-2 activity. It is a promising therapeutic agent against UV-B induced skin disorders and has been studied both in-vitro & in-vivo. It also protects against toxicity from agents such as carbon-tetra chloride or cisplatin **(33, 34).**

Analgesic Effect

Many studies have evaluated the analgesic effect of ginger and its constituents. Its strong analgesic action manifests through cyclooxygenase-1 (COX-1) inhibition. Gingerol and its derivatives, especially [8]-paradol, have been reported to be more potent anti-platelet and cyclo-oxygenase-1 (COX-1) inhibitors than aspirin **(35)**.

Neuro-protective Activity

A daily dose (4 mg/kg) of pure monosodium glutamate (MSG) by i.p. injection for 30 days and subsequent withdrawal caused a significant decrease in epinephrine, norepinephrine, dopamine and serotoninnnn content at all tested areas (cerebellum, brainstem, striatum, cerebral cortex, hypothalamus and hippocampus). Ginger root extracts was found to exert a significant neuroprotective effect by increasing monoamines **(36)**.,

Hepatoprotective Activity

Ginger also has significant hepatoprotective activity. Bromobenzene induced hepatotoxicity is caused by its reactive Phase I metabolites. The efficacy of different doses of ginger extract in alleviating hepatotoxicity was investigated **(37)**. Ginger powder (500-600 mg) taken at the onset of migraine, followed by 4 hourly intake for 3-4 days, is reported to provide relief from migraine attacks **(38)**.

Safety

Ginger is listed in the "Generally Recognized as Safe" (GRAS) document of the US FDA. A dose of 0.5 – 1.0 g of ginger powder ingested 2-3 times for periods ranging from 3 months to 2.5 years did not cause any adverse effects.

Summary

Both the nutritive and the non-nutritive components of the diet play a significant role in the inhibition of carcinogenic process. The non-nutritive constituents of Ginger exert their anti-carcinogenic effect by various mechanisms for instance by their antioxidant properties, or enhancing tissue levels of protective Phase II enzymes so that toxic metabolites of harmful substances are removed. Phytochemicals in spices like ginger, turmeric, mustard and garlic act in more than one way to confer their beneficial effect **(39)**. Studies conducted at the

National Institute of Nutrition (NIN), Hyderabad showed that selected the above mentioned spices and also vegetables stimulate, specifically, the levels of glutathione-s-transferases (GST).

There is a high correlation between the induction of these enzymes and inhibition of carcinogenesis. Since ginger has the potential to inhibit chronic inflammation and arachidonic acid metabolism coupled with antioxidant property, studies were performed to evaluate the stimulation in drug metabolizing enzyme levels in rats, fed ginger through diet. After one month of feeding, significant stimulation of GST activity was seen in liver and lungs.

Frankincense

Most of the published research on Frankincense concentrates on its abilities to counteract inflammmation and chronic diseases such as arthrosis, psoriasis or atopic dermatitis, colitis Crohn's disease, asthma as well as cancer **(40,41)**.

Inflammation

Frankincense's abilty to influence the cascade of events that lead to inflammation in the arachidonic acid metabolism and to inhibit Cyclo and Lipoxygenase enzymes is well documented. Its multpiple effects have led to the recognition that Frankincense is a promising example of a plant suited for multi target synergy therapy **(42)**.

Selected Results

In the treatment of ulcerative or chronic colitis Frankincense is equally effective as common drugs sulfasalazine or mesalazine. It is also effective in preventing colonic fibrosis and/or TNBS induced colitis. The anti-inflammative activity of Frankincense was conferred by boswellic acids inhibiting the leukotriene biosynthesis in neutrophilic granulocytes by a non-redox non-competitive inhibition of 5 lipoxygenase **(43)**. It was shown that Frankincense is effective to treat the inflammation associated with arthritis.

Anti-depressive and Anxiolytic Effects

Incensole causes behavioral as well as anti-depressive and anxiolytic effects and inhibits the activation of **NF kB**, a key transcription factor in the inflammatory response.

Photoaging

Topical application of boswellic acids is a suitable treatment option for skin photo aging **(44,45)**.

Antitumor Effects

The anti-inflammative activity of Frankincense is linked to a pro-apoptotic activity and 5 lipoxygenase inhibition effectively inhibiting and reverting metastasizing. Yet another study showed that Frankincense essential oil appears to distinguish normal from cancer cells and suppresses cancer cell viability in bladder cancer **(46)**.

Cytochrome Inhibition

A search for remedies with inhibitory activity on cytochrome P450 enzymes found B carteri, frereana, sacra and serrata equally effective as non selective inhibitors of the major CYP enzymes 1A2/2C8/2C9/2C19/2D6 and 3A4. Besides inhibiting common Cytochrome P450 enzymes Frankincense components were also shown to have significant hepato protective activity **(47)**.

Characteristic Components

The compounds most studies focus on are boswellic acid and incensole derivatives. Even though there are also some studies which demonstrate similar effects of Frankincense oil which do not have those mentioned components **(46,48)**.

7) Properties of Selected Common Essential Oils of Asian Origin

Basil

Basil essential oil is produced in multiple countries in Asia, among others in Nepal and India. Essential oil of Tulsi, holy Basil, originates form India and also Thailand. Basil is a plant that produces essential oils of extremely varying composition depending on type of plant, location and other factors. With the global distribution of Basil it is difficult to declare one oil specifically Asian, with the obvious exception of Tulsi, which has a composition especially rich in diverse stimulant phenyl propanoids.

Benzoin

Benzoin, derived in East Asia from Styrax benzoe is cherished for its fragrance. The use of Benzoin in aromatherapy is somewhat inhibited as there does not seem to be a universal method to extract the oleo resin. In some instances products on the market are offered diluted with diluents such as Di propylene glycol (DPG) to make the product more manageable (less viscous). On the other hand, undiluted oleoresins are very viscous and difficult to manage for the lay person. In addition it takes a long time for pure oleoresin to dissolve in fatty or in essential oils. In short, its use is limited as it requires special preparation to work with it.

One of the best ways around this is to prepare a stock solution, where a Benzoin is transferred into a suitable essential oil, for instance, Lavender essential oil and given time to dissolve.

In French style aromatherapy Benzoin is credited with the ability to speed up wound healing and tissue formation and therefore recommended for different forms of dermatitis, acne, eczema, psoriasis and other skin ailments.

Camphor

Traditionally used in Chinese medicine. In western style aromatherapy Camphor essential oil is not commonly used. Camphor oil is a general tonic and stimulant for the cardio vascular and respiratory systems. It is used topically for rheumatic and neuralgic pains as well as contusions. For higher dosages the same cautions apply that are described in the literature for the use of essential oils with high ketone content.

Cassia

Cassia, Chinese Cinnamon yields an oil similar to the well known Cinnamon of Ceylon. In comparison it has only traces of eugenol but a sizable proportion of coumarin. Compared to Cinnamon of Ceylon its taste is slightly bitter.

Its therapeutic uses are similar to those of Ceylon Cinnamon bark or even broader. It counteracts many different types of intestinal infections (including tropical infections), toxicity buildup, discharge, bacterial cystitis and also lack of energy, especially for men.

Citronella

There are two species commonly referred to as yielding Citronella oil: Cymbopogon nardus as source for Citronella of Ceylon and C. winterianus as Citronella of Java.

Different from Lemongrass, Citronella oils contain the aldehyde citronellal (instead of Citral).

The main areas of application of Citronella oils in aromatherapy is as spasmolytics and anti-inflammative agents especially for rheumatoid and/or arthritic symptoms.

Geranium, Chinese

Pelargonium asperum from China is specifically mentioned in L'aromatherapie exactement. Being cultivated commercially for apparently quite some time in China the oil has a slightly different composition from other Geranium oils, i.e. Madagascar or Egypt. It contains more citronellol and less geraniol than the latter. Compared to other Geraniums it has a notable Rose like fragrance and is considered to have a more pronounced antibacterial effect.

Ho

Ho oil is yet another oil from the Cinnamomum camphora tree. It is Asia's version of an oil with a very high linalool content, the Asian Rosewood one might suggest.

It provides good tonifying properties and is effective against viral, bacterial and fungal pathogens.

Lemon and Lime

Citrus trees are thought to be originating from North India, Myanmar and the Yunnan province area of South East Asia.

The therapeutic quality of these plants is driven by their ability to induce Phase II liver detoxification enzymes. This has been acknowledged by traditional healing systems which prescribe the peel for detoxification and elimination.

Citrus essential oils are most often produced by so called cold pressing. The result of this specific production method is that molecules from the peel with higher molecular weight can be present, especially coumarin or its derivatives.

The main terpenoid component is (+) limonene, which has attracted significant research. It has been demonstrated that (+) limonene has outstanding antiviral effects but apparently also antitumor effects. Lemon essential oil is a staple of any aromatherapy apothecary, mainly for its antiviral effects and its ability to induce detoxification.

Lemongrass

An archetypical Asian essential distilled from the species Cymbopogon flexuosus. The oil of Cymbopogon citratus is also often referred to as Lemongrass, whereas in the Grasse trade it has also been called "Indian Verbena."

The oils provide the typical therapeutic synergy of the citrals (neral and geranial). Blended with other essential oils they are used in aromatherapy as digestive tonics, vaso dilators, anti-inflammative and sedative agents. This makes them uniquely suited to address autonomic nervous system imbalances. The combination of neral and geranial present in Lemongrass oil induces Phase I and Phase II liver detoxification enzymes.

Palmarosa

Palmarosa essential oil is one of the archetypical Asian essential oils derived from grasses. (along with the Lemongrass, Citronella and others)

Its high geraniol content gives this oil an appealing fragrance and a powerful antiviral quality. Its plane of activity is that of wei qi, but this oil also addresses issues that go somewhat deeper, with a ying qi component. The oil is best used topically and blended. In aromatherapy it has also been ingested to treat acute flairs of Dengue fever (in combination with Bay Laurel, Tea Tree and Cinnamon).

Patchouli

Patchouli has a composition not found in any other plant. In French style aromatherpay the oil is credited as an agent appropriate for a range of skin and tissue conditions. It tonifies veins and is recommended for eczema, acne and dermatitis conditions of different origins.

Ravintsara (Cinnamomum camphora, cineol type)

Notwithstanding traditional uses of the Cinnamomum camphora tree it was French style aromatherapy which created the awareness for the immense usefulness of this essential oil. Ravintsara is an oil characterized by a synergy of nonirritant monterpenoids. It tonifies wei qi, supporting the organism in defending against infectious disease. Its excellent antiviral properties have been sufficiently described. In aromatherapy it is the agent of choice - in connection with the fatty oil of Calophyllum inophyllum in the treatment of shingles (Herpes zoster). As a matter of fact the treatment of shingles with Ravintsara is probably significantly more effective than available conventional treatment.

Spikenard

The composition is dominated by sesquiterpenes. Growing in higher elevations in Nepal and India it is gathered in the wild and color and composition of the essential oil seem to be quite variable. The oil has historically been esteemed, probably as a result of the combination of relaxing and sedative effects of its valerian like components and also because of the ionone, violet like aspects of the fragrance. In aromatherapy Spikenard oil is used as a powerful sedative and as a key ingredient in regenerative skin care.

Wintergreen

Gaultheria fragrantissima is the Himalayan species of the genus Gaultheria and the source for Nepalese (and probably other Asian) Wintergreen oils. It differs from oil distilled from Gaultheria procumbens in having a slightly more diverse composition with less methyl salycilate (99% in G. procumbens) and a little more of other components. It is traditionally used as an antispasmodic and to ameliorate rheumatism and other types of inflammation.

Ylang - Ylang

An essential oil recovered from the flowers of the Canaga odorata tree, dominated by the balsamic and floral aromas which arise when terpene and phenylpropane synthesis contribute to the final composition. Benzyl benzoate and para cresol methyl ether are among the characteristic components.

Ylang Ylang essential oil is considered to be sexually tonifying. It is generally equilibrating. Clearly its use in aromatherapy is determined by an individual liking of the fragrance.

8) Outlook

Given the considerable research demonstrating the beneficial effects of many spices of Asian origin it can be expected that similar to past developments the aromatherapy community will take up these extracts and explore their practical benefits. Plants which might receive renewed attention are Cardamom, Cinnamon (antidiabetic components), Ginger and especially Turmeric (Curcuma longa, xanthorrhiza).

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Table 3: Molecular Targets for Essential Oils and Aromatic Extracts (for references see 4)

Nuclear Factor - kappa B (NF kB)

NF kB is a family of proteins which generally occur in dimeric form. Under resting conditions these dimers reside in the cytoplasm of the cell. There are many stimuli which can activate the **NF kB**: free radicals, inflammatory stimuli, cytokines, carcinogens, tumor promoters, endotoxins, gamma radiation (x-rays), and ultra violet light.

Once activated, it moves to the cell nucleus and it induces the expression of more than 200 genes. Specifically genes that have been shown to suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemo resistance, radio resistance and inflammation. Many of the genes that are activated have been linked to the establishment of the early and late stages of aggressive cancers. Current thinking is that suppressing NF kB activation is one way by which many secondary metabolites exercise their antitumor properties.

Activator protein-1 (AP-1)

Many stimuli, most notably serum, growth factors, and oncoproteins, are potent inducers of AP-1 activity; it is also induced by a variety of environmental stresses, such as UV radiation. AP-1 activation is linked to growth regulation, cell transformation, inflammation, and innate immune response.

Cell cycle

Several proteins are known to regulate the timing of the events in the cell cycle. The loss of this regulation is the hallmark of cancer. Major control switches of the cell cycle are the cyclins and the cyclin-dependent kinases.

Dysregulation of the cell cycle check points and overexpression of growth-promoting cell cycle factors such as cyclin D1 and cyclin-dependent kinases (CDK) are associated with tumorigenesis. Several dietary agents including curcumin, resveratrol, genistein, dietary isothiocyanates, apigenin, and silibinin have been shown to block the deregulated cell cycle in cancers.

Cyclin D1 has been shown to be overexpressed in many cancers including breast, esophagus, head and neck, and prostate. Curcumin has been shown to inhibit progression of the cell cycle by down-regulating the expression of cyclin D1 at the transcriptional and posttranscriptional level.

Apoptosis

Apoptosis helps to establish a natural balance between cell death and cell renewal in mature animals by destroying excess, damaged, or abnormal cells. However, the balance between survival and apoptosis often tips towards the former in cancer cells. Several reports published within the last decade showed that activation of NF-kB promotes cell survival and proliferation and down-regulation of NF-kB sensitizes the cells to apoptosis induction.

Several phytochemicals that are known to inhibit NF-kB or AP-1 activation can significantly suppress cell proliferation and sensitize cells to apoptosis induction.

Cell survival kinase Akt

The serine/threonine protein kinase Akt/PKB is the cellular homologue of the viral oncogene v-Akt and is activated by various growth and survival factors.

Tumor-suppressor gene p53

p53 is a tumor-suppressor and transcription factor. It is a critical regulator in many cellular processes including cell signal transduction, cellular response to DNA-damage, genomic stability, cell cycle control, and apoptosis. adulthood.

Growth factors signaling pathways

Growth factors are proteins that bind to receptors on the cell surface, with the primary result of activating cellular proliferation and/or differentiation. Some of the growth factors implicated in carcinogenesis are epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), transforming growth factors (TGF)-a and -b, erythropoietin (Epo), insulin-like growth factor (IGF), interleukin (IL)-1, 2, 6, 8, tumor necrosis factor (TNF), interferon-g (INF-g) and colony-stimulating factors (CSFs).

Chemokines and Metastasis

Chemokines are small, chemotactic cytokines that direct migration of leukocytes, activate inflammatory responses, and participate in regulation of tumor growth.

Tumor necrosis factor (TNF)

Tumor necrosis factor (TNF), initially discovered as a result of its antitumor activity, has now been shown to mediate tumor initiation, promotion, and metastasis. In agreement with these observations, mice deficient in TNF have been shown to be resistant to skin carcinogenesis.

Signal transducer and activator of transcription (STAT)

STAT proteins are signaling molecules with dual functions that were discovered during studies on interferon (IFN)-dependent gene expression.

Cyclooxygenase-2 (COX-2)

Cyclooxygenases are prostaglandin H synthases, which convert arachidonic acid released by membrane phospholipids into prostaglandins. Two isoforms of prostaglandin H synthase, COX-1 and COX-2, have been identified. COX-1 is constitutively expressed in many tissues, but the expression of COX-2 is regulated by mitogens, tumor promoters, cytokines, and growth factors. COX-2 is over expressed in practically every premalignant and malignant condition involving the colon, liver, pancreas, breast, lung, bladder, skin, stomach, head and neck, and esophagus. Depending upon the stimulus and the cell type, several transcription factors including AP-1, NFIL- 6, NF-kB can stimulate COX-2 transcription. Thus, all the dietary agents that can suppress these transcription factors have the potential of inhibiting COX-2 expression.

Lipoxygenase (LOX)

LOXs are the enzymes responsible for generating leukotrienes (LT) from arachidonic acid. There are three types of LOX isozymes depending upon the different cells and tissues they affect. 15-LOX synthesizes anti-inflammatory 15-HETE; 12- LOX is involved in provoking inflammatory/allergic disorders; and 5-LOX produces 5-HETE and LTs, which are potent chemoattractants and lead to the development of asthma. Aberrant arachidonic acid metabolism is involved in the inflammatory and carcinogenic processes.

Inducible nitric oxide synthase (iNOS)

Nitric oxide synthase is responsible for the release of the gaseous free radical nitric oxide during the formation of L citrulline from L-arginine. Excessive and prolonged iNOS mediated NO generation has been linked with inflammation and tumorigenesis.

Mitogen-activated protein (MAP) kinases

In addition to NF-kB and Akt pathways, MAPK pathway has received increasing attention as a target molecule for cancer prevention and therapy.

DNA methylation

DNA methylation is a covalent modification resulting in the addition of a methyl group to the cytosine ring. Hypermethylation leads to gene silencing through the suppression of transcription.

Figure 3: Influence of Plant Aromatics on Cancer and Inflammation Related Molecular Targets

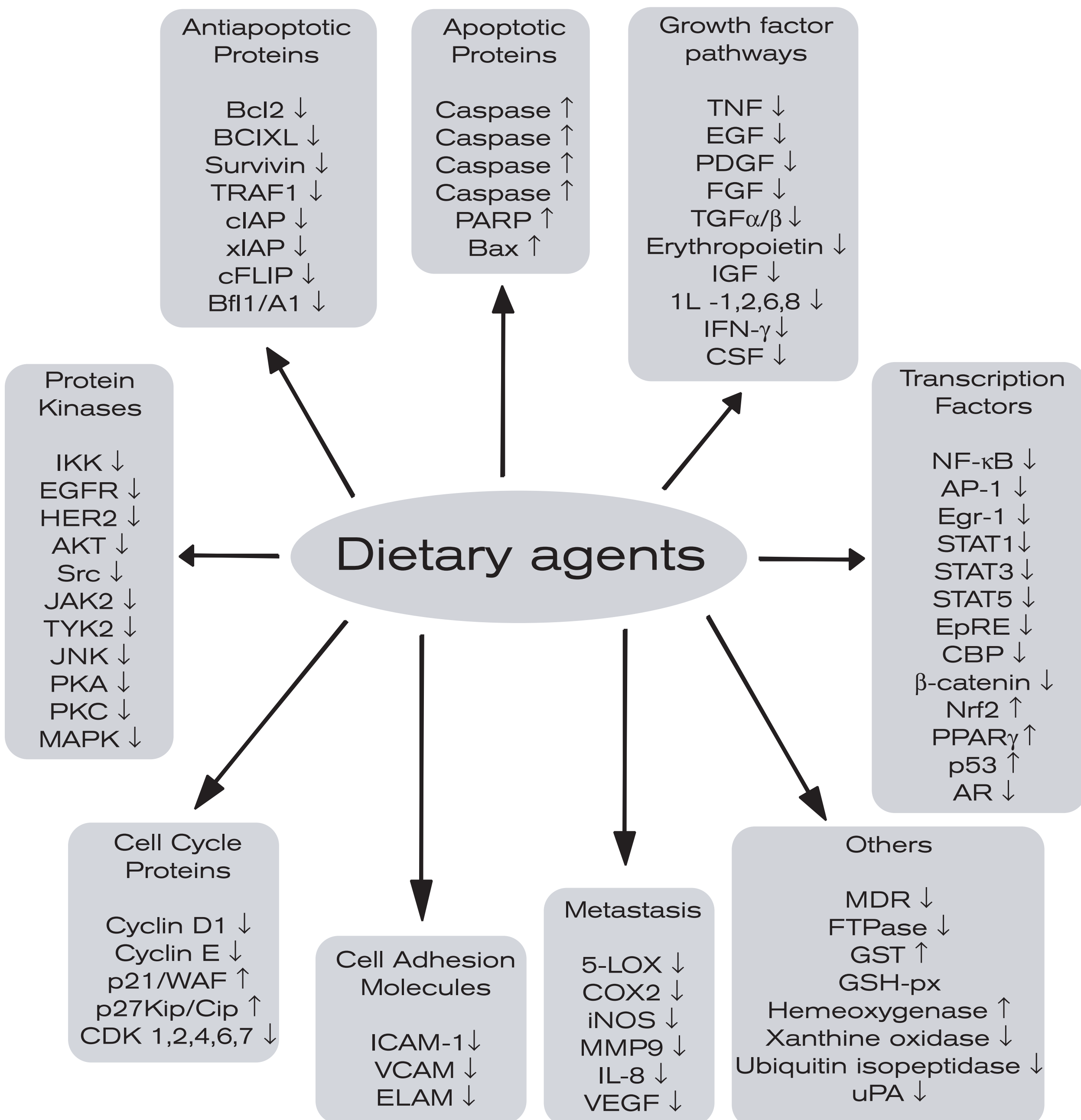

Figure 4: The Molecular Targets affected by 6-Gingerol

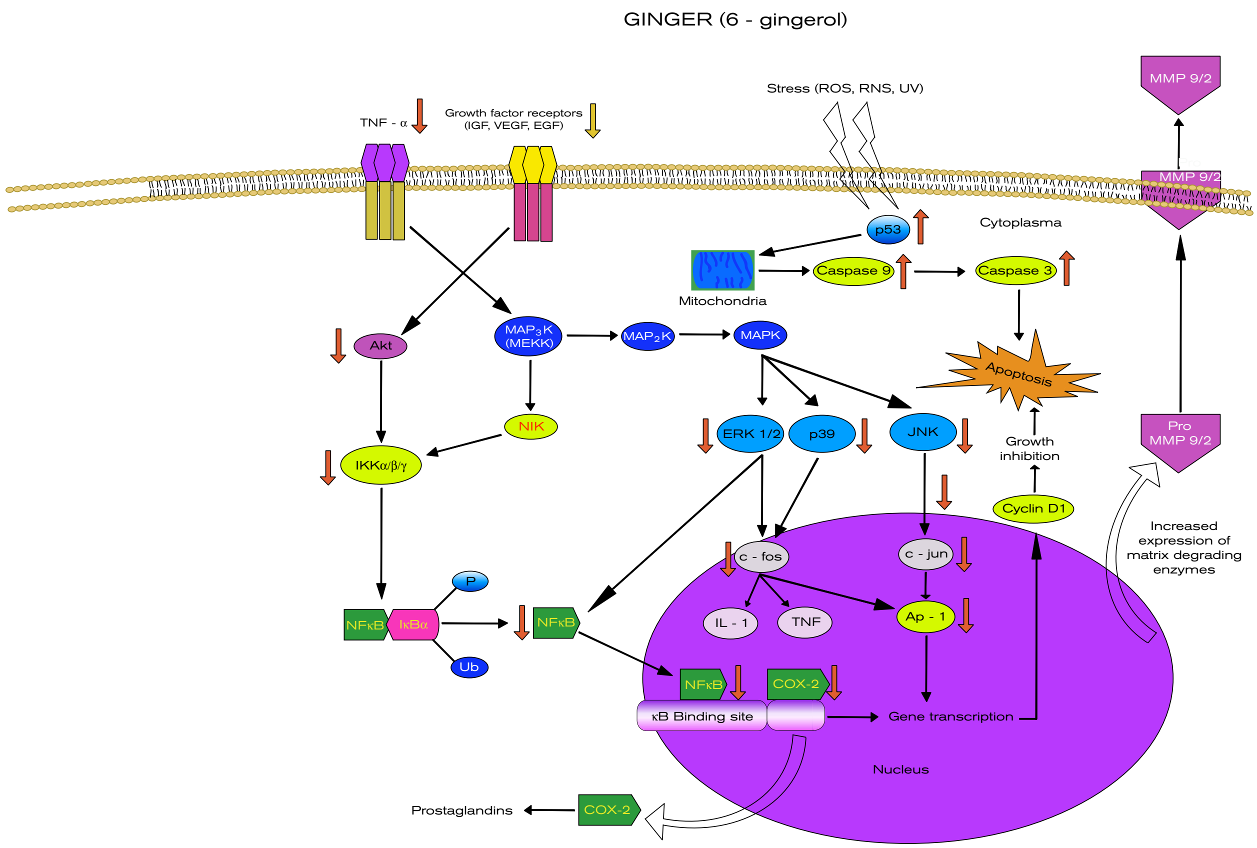

Figure 5: Arachidonic Acid Metabolism