Project no. 311919

StarTree

Multipurpose trees and non-wood forest products a challenge and opportunity

Start date of project: 1 November 2012

Duration of project: 4 years

Collaborative Project

FP7-KBBE-2012-6-singlestage

D5.2 Report on new forest products and promising chemical substances

Due date of deliverable: **30 June 2014**

Actual submission date: **18 June 2015**

Organisation name of lead contractor for this deliverable: **Universität Hamburg**

Dissemination level: **PU**

Multipurpose trees and non-wood forest products, a challenge and opportunity www.star-tree.eu

This project has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 311919

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Reference

Becker VK, Fromm J, Mantau U, 2015. Report on new forest products and promising chemical substances. Deliverable D5.2 of the StarTree project.

Executive summary

Due to synthetic medicines traditional pharmaceutical knowledge gradually decreased over the last few decades. However, the developing trend proves an increased interest of society in herbal medicines for self-medication and as a complement to a conventional medical approach (not as a replacement). The pharmaceutical value of a plant is defined by the type, amount and mixture of secondary metabolites (SM). Stimulating factors for the SM synthesis are defence and attraction. Therefore, wild plants show a higher SM production, compared to cultivated individual plants. NTFPs form an ideal source for promising chemical substances. This report gives an overview on typical botanicals used in traditional medicine and on the pharmaceutically active compounds. Challenging for the developing market of phytopharmaceuticals is the slow and partially even lacking adaption of European laws and policies. Black cherry (*Prunus serotina*) is a so far unexploited recurrent species in German forests containing a here proven significant content of amygdalin which is currently rediscovered in cancer research. Thus, *Prunus serotina* forms an innovative NTFP with untapped potential. A harvest field trial has been carried out in summer 2014 showing methodological hurdles, whereas the chemical analysis is promising. Altogether the unused and forgotten potential of chemical substances in NTFPs is tremendous but legal frameworks and monetary barriers often slow down evolution of products and the market itself.

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1 Basics of natural products

Classifying NTFPs in product lines, such as edibles, specialty wood products, floral greens and medicinal and dietary supplements, it can be said that the latter is the highest value segment of the NTFP industry in the USA (Greene et al., 2000). This demonstrates the weighting and character of the NTFP market in a western country. According to records, as early as in the 26th century BC approximately 1000 plant-derived substances were used for medication, including oils of cypresses, cedars and myrrh. How effective and important the treatment with herbal medicine actually is, proves the steady application until these days (Borchardt, 2002; Cechinel-Filho, 2012). Society's interest in medicinal and dietary supplements grew throughout the last decades (Häußermann, 1997). 65% of the world`s population is deepening its knowledge in herbal medicine for their primary health care, mainly also in developed countries (Farnsworth et al., 1985).

Whereas in former times food was rated according to its energy value, nowadays the nutritional value is of great interest in developed countries. Food as medicine gains in importance (Pieroni & Price, 2006). Besides essential minerals and trace elements the nutritional value is defined by **secondary metabolites**. Depending on the type, amount and composition of the secondary metabolites, the dosage form can vary. Apart from consuming the plant as a whole as food, it can be used as an infusion, decoction, maceration, succus (sap), tincture, extract, aromatic water, syrup, spirit, suppository, ointment or in the form of medicinal products, such as pills or tablets (Bäumler, 2007).

Hereafter, this report will focus on the approximately 100 000 secondary metabolites of plants so far known (Afendi et al., 2012).

1.1 Basic chemistry

The activity of an organism depends on two metabolic pathways, namely primary and secondary metabolism. The primary metabolism is involved in vitally important functions, such as maintenance and reproduction (growth, energy production, transmission and distribution, turnover etc.). The secondary metabolism does not directly affect maintenance and reproduction of an organism; however, the products of these metabolic pathways, referred to as **secondary metabolites**, are of high importance for the survival of an organism (Herbert, 1989).

There is a transition zone between the two groups, in which substances are not clearly defined to be primary or secondary metabolites (Adam et al., 2014; Heldt et al., 2008; Ludwig-Müller & Gutzeit, 2014). Typical primary substances are proteins, DNA/RNA (Nucleotides), carbohydrates and fats. An exemplary transition zone representative is lignin, a phenolic polymer and main component of wood: lignin is essential for several plant tissues and typical enzymes of primary metabolic pathways are involved in its synthesis. However, it also functions as a repellent – a typical purpose of secondary metabolites (Iason, 2012). Further functions – apart from pathogen and herbivore defence – include protection against UV radiation and transpiration, which can be summarized under the general heading of "**defence**". Together with the task of "**attraction**" (for pollination & seed dispersal), these two constitute the main purposes of secondary metabolites, which play an important role in the interaction between plants and their environment (Dixon, 2001; Ludwig-Müller & Gutzeit, 2014).

The chemical elements of primary and secondary metabolites can be divided in two groups: non-mineral and mineral. Carbon (C), hydrogen (H) and oxygen (O) are non-mineral and enter a plant through the process of photosynthesis (via carbon dioxide (CO_2) and water (H_2O)) (Dunn, 2007). Mineral nutrients come from soil and are absorbed through roots; differentiation is made between macro- and micro nutrients.

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Potassium (K), nitrogen (N) and phosphorus (P) are macronutrients, which are absorbed by plants in larger amounts. That is why fertilisation is often required in commercial cultivation. Sulphur (S), calcium (Ca) and magnesium (Mg) are also referred to as macronutrients and also needed in larger amounts; however, they usually occur in sufficient quantities due to decomposition and chemical reactions of lime. Micronutrients are only used in small quantities, these are namely iron (Fe), manganese (Mn), copper (Cu), boron (B), molybdenum (Mo), chloride (Cl) and zinc (Zn) (Arora, 2010; Dunn, 2007).

Depending on the occurrence of these elements, the production of **secondary metabolites** is affected. However, there are several biotic and abiotic factors that affect not just the biosynthesis but also the accumulation of secondary metabolites, such as (You et al., 2012):

- chemical composition of atmosphere
- pathogen attacks, mechanic stimulus and herbivory
- temperature
- ultraviolet radiation
- hydric stress
- soil influence and its nutrients

As earlier mentioned, the main purpose of secondary metabolite production is **defence** and **attraction**. Pine needles contain certain substances which disturb the digestive system of mammals (Adams et al. 1992) and its essential oil effectively defends bacteria (Schales et al. 1993). Flowers emit compounds which attract pollinators or even supportive organism for indirect defence (Iason, 2012). Anthocyanins and monoterpenes even serve both purposes, being present in foliage they defend, being present in flowers they attract (Wink & Schimmer, 2010).

1.2 The importance of secondary metabolites

Being used as medicine and food, plants play an important role in the history of mankind. Even though selective cultivation mostly replaced gathering wild plants, the beneficial potential of some products disappears through cultivation. This applies particularly where the potential of a good is not defined in terms of energy but by constitution and content of nutrient content, namely the content of **secondary metabolites**. Grown under wild conditions, plants often contain a higher amount of secondary metabolites (Kindscher et al., 2014). Wild raspberries are just one of several examples for holding an increased antioxidant capacity compared to their cultivated variation (Çekiç & Özgen, 2010). This propagates the utilisation of NTFPs as a source of promising chemical substances. The reasons lie above all in:

- cultivar selection and production practices usually focus more on energetic yield than on nutritional value,
- minor stress during growth makes the plant produce less secondary metabolites (no need for defence mechanisms due to pesticides and no lack of nutrients due to fertilizer) (Kindscher et al., 2014).

Goods containing secondary metabolites are characterised by their considerable impact on human health through small amounts of these chemical constituents or a mixture of those. Among others, plants containing notable types and amounts of secondary metabolites are mainly used in the field of pharmaceuticals and foodstuff. However, the effective impact on the human body is defined in terms of opportunities and risks (Watzl & Leitzmann, 2005). Before the production of synthetic chemicals the chemicals of plants were used in response to great demand. Plant-based dye for instance derived from shikonin, flavours from vanillin, fragrances from essential oils, stimulants from nicotine, hallucinogenes from morphine, poisons from coniine and medicine from quinine (Roberts und Wink 1998).

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2 Secondary metabolites in NTFPs

2.1 Classes of substances

Several classifications of secondary metabolites exist, based upon chemical structure, solubility (lipophilic/ hydrophilic) or biosynthetic origin (Verpoorte & Alfermann, 2000). The classification used here originates from built in primary substances since no generally accepted system exists (Figure 1).

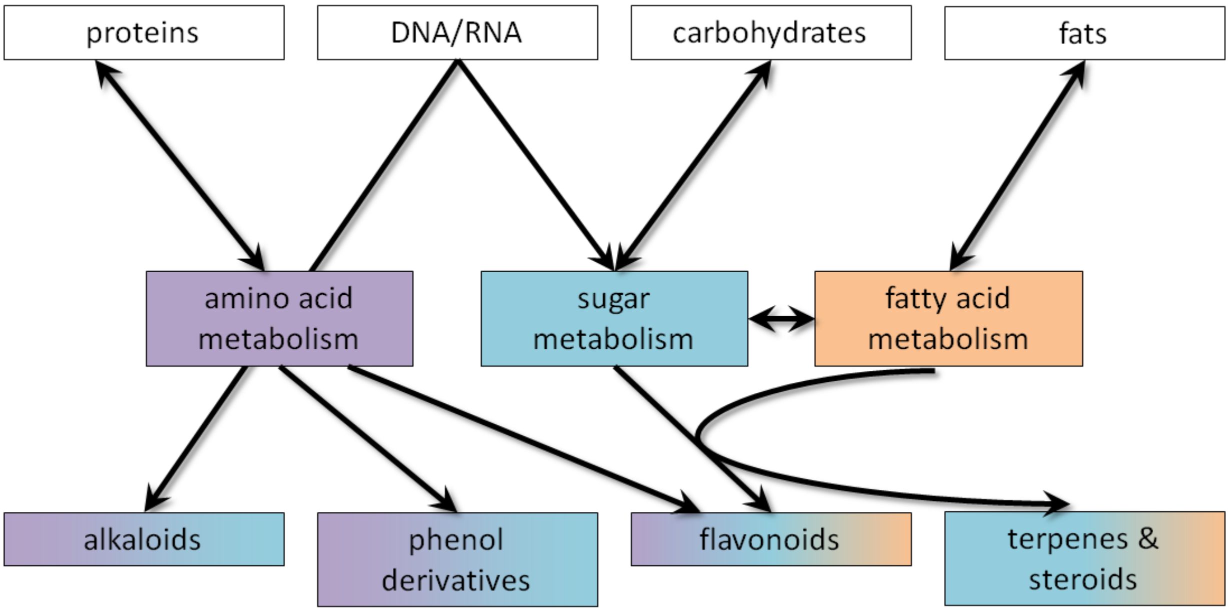

Figure 1: Simplified schematic picture of secondary metabolites sorted by the primary product they are derived from (Ludwig-Müller & Gutzeit, 2014). Arrows indicate reversible and irreversible metabolic pathways.

This differentiation results in four main classes of secondary metabolites (alkaloids, phenol derivate, flavonoids, terpenes & steroids) which will be defined and described in the following section.

Alkaloids are a group of approximately 100.000 substances. These nitrogen containing metabolites show their pharmaceutical effect even with a small dose, which is mostly exhilarating, excitatory and soothing (Luca & St Pierre, 2000). Since small doses are usually sufficient to reach desired effects, higher doses are often toxic. Extraction by methanol is the most common way to isolate alkaloids from plant tissues (Breitmaier et al., 2005). Biosynthesis pathways are complex and only partly well researched. An example for complexity is the occurrence of alternatives within one metabolic pathway, for instance depending on the availability of resources (Ludwig-Müller & Gutzeit, 2014). A distinction is made between two main groups within alkaloids: heterocyclic and non-heterocyclic compounds. Primarily heterocyclic compounds are of high importance for promising chemical components (Facchini, 2001) The here selected groups with detailed descriptions are pyrrolizidine alkaloids, quinolizidine alkaloids, indolizidin alkaloids, indol alkaloids. This arrangement in groups originates from the intermediates of their biosynthesis, in case of alkaloids, these are mainly amino acids (Facchini, 2001).

Pyrrolizidine alkaloids (PAs) require ornithin, valin and leucin as preliminary stages (intermediates). PAs act mutagenic and carcinogenic. Honey from plants containing PAs is considered a potential threat to health (Edgar et al., 2002). So far – even in small doses – no beneficial effect on the body has been discovered (Ludwig-Müller & Gutzeit, 2014).

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Quinolizidine alkaloids (QAa) require lysin and cadaverin as precursors. *Cytisus scoparius* contains serious high amounts of the QA named sparteine. Especially the root is used in traditional chinese medicine (TCM) where it is called “Ku shen” and used against liver disorders, dysentery or edema (Ho et al., 2009). *Lupinus luteus* contain considerable amounts of lupinine, which causes the natural bitter taste of the *Lupinus* species (Gossauer, 2006). Lupinine is claimed to be harmful to health (Ludwig-Müller & Gutzeit, 2014).

Indolizidin alkaloids, the precursor of which is lysin, have strong pharmaceutical effects. In laboratory experiments, the swainsonine appears to be an anti-cancer drug (Klein et al., 1999; Oredipe et al., 2003; Sun et al., 2007). Any plant which produces swainsonine is named as “locoweed”. Locoism (swainsonine toxicosis) is reported in cattle, sheep and horses consuming these plants on range land (Jones et al., 1997). TCM uses *Astragalus membranaceus* due to its alkaloid content as a treatment for kidney disease, arteriosclerosis or stimulation of the immune system (Matkovic et al., 2010; You et al., 2012).

Indol alkaloids with the precursors tryptophan and tryptamin form the largest group of alkaloids (Seigler, 1998). Prubiaceae, Loganiaceae and Apocynaceae are typical indol alkaloids containing families in plant kingdom. Indol alkaloid cinchona is found in Cinchona bark (family Rubiaceae) and tradionally used as muscle relaxant in case of shivering, for instance caused by malaria (Seigler, 1998). Serotonin has a wide range of application to the human body, especially in cardiovascular system, gastrointestinal tract, nervous system and psyche. A high concentration of serotonin is predominantly found in walnuts (Bergmann et al., 1970).

The group of **phenol derivatives** is characterised by the dominant group of flavonoids. Half of the 8000 known phenolic compounds are flavonoids (Harborne 1996). The metabolic route named shikimic acid pathway including the initial substrate amino acid phenylalanine forms – among others – the basis of production for phenols. The following section will point out most relevant representatives.

Cumarin itself is claimed to be poison, according to *Dangerous Substances Directive*. However, its derivates are used at low dosage levels for blood-clotting inhibition, higher doses cause internal bleeding with lethal outcome and therefore used as rodent-control (Lüllmann et al., 2010). *Galium odoratum* is a natural source of cumarin.

Rosmarinic acid is easily absorbed by skin with an anti-inflammatory effect and easing sports injuries (Bajaj, 1994). Rosmarinic acid is a complex phenolic compound (Ludwig-Müller & Gutzeit, 2014).

Resveratrol, first isolated from medical plant *Veratrum grandifloru* is of high importance in the field of phytopharmaceuticals. Resveratrol is a phytoalexin, highly concentrated found in grapes. The isolated substance showed cancer chemopreventive activity (Jang, 1997). Also incidence of Alzheimer disease is influenced by this secondary metabolite out of red vine (Ono *et al.*, 2008). Resveratrol is part of the defence mechanism of plants and is not synthesized under stress-free conditions (Seigler, 1998).

Anthocyanins belong to the big group of flavonoids (Andersen, 2001). Even in higher concentrations they are not of greater risk to human life (Wallace, 2013). Having potential health-promoting properties, such as an antioxidant effect through inhibition of free radicals, this group is already of high interest for industry (Andersen, 2001).

Proanthocyanidins are mainly present in woody plants, especially in the families Rosaceae and Fagacea (Bäumler, 2007). Rhizomatous root of Tormentil`s (*Potentilla erecta,* family Rosaceae), dried and grinded or used as an extract, kills germs and viruses. Usually used to relieve inflammation of the mouth and throat, tormentil`s tannin content of the sap additionally allows the traditional utilisation of dying in yellow, red and brown colours, which depends on earlier treatment of the material (Pieroni & Vandebroek, 2009; Tomczyk & Latté, 2009). High contents of proanthocyanidins are also found in cortex (bark) of *Quercus petraea* and *Q. pubescens* (Dingermann et al., 2002). Cortex of *Q. ilex* showed high antibacterial activity,

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for instance against bacteria food contaminating species such as Salmonella *Typhimurium* and *Listeria monocytogenes*. Additional fungicidal potential of the compounds was observed which was even higher than the commercial fungicides used as control (Karioti et al., 2011). Alchemilla (*Alchmilla vulgaris* and *Alchemilla xanthochlora*), commonly known as "lady's mantle" and European blueberry (*Vaccinium myrtillus*) also provide a high amount of proanthocyanidins (Dingermann et al., 2002).

Terpenes in general are intoxicating substances, such as cannabinoids. They are separated into two groups, depending on whether the substance is essential or not essential for plants life (Ludwig-Müller & Gutzeit, 2014). Not essential substances might give an advantage in certain circumstances, however even without these substances, plants would survive. The class of terpenes are – from a purely chemical point of view – divided in several steps. The basic terpene molecule (isoprene) contains five carbon atoms (C5), two basic terpene molecules form the second step (C10), three basic terpene molecules form the third step (C15) and so forth (Breitmaier 2012). Low molecular terpenes (C5 to C15) are volatile substances of essential oils. Besides antimicrobial activity, terpenes show manifold effects, mostly depending on the size of the molecule. Forskolin (found in *Coleus forskohlii*) is just one of many pharmacologically active substances in this group of secondary metabolites, considered to be applied in case of overweight, asthma or heart diseases (Kavitha et al. 2010).

Steroids are derived from triterpenes (C30). Through glycosylation they are converted into saponin, a secondary metabolite which is not only important in the field of phytopharmaceuticals, but also in organic housekeeping (Arnason, 1995). The sap of common soapwort (*Saponaria officinalis*) is traditionally used as gentle soap. Same intended use due to its high saponin content has the soap bark tree (Quillaja *saponaria*) (Horton 2014). In the human body renal function is stimulated and the effect of other pharmaceutic active substances is supported by saponin (Francis et al. 2002).

Alkaloids, flavonoids and other phenolics and terpenes occur in every type of plant; however, there are also substances which only occur in specific families. Glucosinolates, for instance, almost exclusively appear in the family of Brassicaceae (Luca & St Pierre, 2000). Glucosinolates and cyanogenic glycosides hold very similar intermediates and mechanism of action, however, from the evolution point of view, they originate from different directions (Ludwig-Müller & Gutzeit, 2014). Both belong to the group of preformed defence substances, including the same mechanism of action.

The here described effects on the human body caused by a specific secondary metabolite do not necessarily reflect what a plant – predominately containing that substance – might cause. The medical effect of a plant is more likely described by the mixture of secondary metabolites, and therefore by the interaction of those (Ludwig-Müller & Gutzeit, 2014).

2.2 Traditional use of trees in temperate zones

In trees, everything not being a structural polysaccharide (cellulose / hemicellulose), lignin or nutrients and regulators is referred to as secondary metabolites. Amounts vary depending on location, season, species and even individuals itself (Forestry Commission, 2001). No regard has been paid to these substances lately; traditional uses were buried in oblivion and were replaced by synthetic substances easy to purchase in supermarkets. With a growing environmentalism and trust in nature, society supports numerous opportunities for adding value to forest products. The following section describes the most common traditional utilisations of secondary metabolites in European trees (Table 1).

2.2.1 European barberry (Berberis vulgaris)

European barberry is used for weaning from opium or morphine, additionally weak gall bladder function is supported and liver dysfunction can be balanced. Roots are used for tea preparation, tincture or extract, picking takes place in September/October. Active metabolites in the roots are isoquinoline and protoberberine (alkaloids against parasitic diseases), oxalic acid, tannin and resin, whereas the berries are

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high in vitamin C (ascorbic acid), anthocyanins, caffeic acid derivatives and organic acids. In this combination of active ingredients, berries act appetising and support immune system. Unripe fruits stimulate the intestinal peristaltic due to their berberine content (alkaloid) (Bäumler, 2007; Imanshahidi & Hosseinzadeh, 2008; Ivanovska & Philipov, 1996).

2.2.2 Common broom (Cytisus scoparius)

Quinolizidine alkaloids (mainly sparteine) determine the effect of this shrub. Broom is toxic (risk of overdosage) with a positive impact on tachycardic arrhythmia and cardio-vascular disorder (Raja et al., 2007).

2.2.3 Birch (Betula sp.)

Young birch tree leaves are usually collected in the months May and June. At that point, the dominant ingredients are hyperoside, quercitin and myricetin (Bäumler, 2007). Besides that, triterpenes, saponins, tannins and ascorbic acid complete the constellation of secondary metabolites which is characteristic for birch leaves (Ossipov et al., 1996; Salminen et al., 2004). Together they act as a blood cleansing agent by stimulating the diuresis. The driving force is the high content of flavonoids (Dallenbach-Toelke et al., 1986). Ascorbic acid inhibits platelet aggregation and thus reduces the risk of thrombosis (Bäumler, 2007).

Another form of dosage is the birch tar or birch pitch. The bark needs to be distilled (pyrolysis), using temperatures up to 400°C in a sealed container for several hours. The thus produced product contains approximately 6 % of phenols (Seidel, 2012). Used like an ointment, phenolic ingredients like guaiacol, cresol and catechol ease chronic skin conditions, however at the same time they might irritate sensitive skin. The production process carries a risk of hydrocarbon carcinogens formation. thatis why it is not recommended these days (Bäumler, 2007). Traditional use of birch tar is for gluing (Pollard & Heron, 2008).

2.2.4 Sweet chestnut (Castanea sativa)

The foliage is used for tea preparation, consumed up to 3 times a day in case of upper respiratory tract infection. Active ingredients are tannins, flavonoids and triterpenes (Bäumler, 2007).

2.2.5 Oak (Quercus robur)

Oak bark contains 10 to 20 % of tannins; other dominant classes are flavonoids (for instance quercetin) and triterpenes (Ciesla, 2002). Oak bark is applied both, internally and externally, side effects do not occur from overdosage. Using the chopped bark as tea, it usually eases diarrhoea and acts anti-inflammatory and antiviral (Ciesla, 2002). Taking a bath with 10 to 20 g per litre of water soothes chronic inflammations and inflammatory skin diseases, eczemas and haemorrhoids (Bäumler, 2007).

2.2.6 European ash (Fraxinus excelsior)

Both, bark (Fraxinus cortex) and foliage (Fraxinus folium) of ash are used for medication. Cortex contains hydroxycoumarins, iridoids and tannins as major components with pain-relieving, anti-inflammatory and antiexsudative effect (Eyles et al., 2007). Leaves are preferably used as tea, containing flavonoids, iridoids, tannins, triterpenes, steroids, mannitol and up to 20 % of mucins (Bäumler, 2007).

2.2.7 Alder buckthorn (Rhamnus frangula)

Frangulae cortex is harvested in May and June. In order to get rid of its emetic character, the bark is stored at least for a year (Bäumler, 2007). The active ingredients are hydroxyanthracene derivatives for the treatment of constipation (EFSA NDA Panel, 2013).

2.2.8 Spruce (Picea sp.)

Needle oil is the most common drug from spruce. Bases are fresh needles and plant tips from both, Picea and Abies. With contents up to 45%, the major component of the needles is bornyl acetate and borneol (1 to 8 %). Beside these, limonene, camphene, β-Phellandrene, α-pinene and β-pinene, myrcene, terpene

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hydrocarbons, flavonoids and ascorbic acid occur in the needles of spruce (Bäumler, 2007). The combination of these secondary metabolites has a highly antimicrobial effect against bacteria and *Candida albicans* (Higley & Higley, 2005).

2.2.9 Ginkgo (Ginkgo biloba)

Ginkgo biloba folium is used for drug production. The leaves are harvested right before leaf fall at the end of the summer, when active ingredients content is the highest, (Kleijnen & Knipschild, 1992; Sticher & Steinegger, 2010). The utilisation of leaves originate from traditional Chinese medicine (TCM), where also the seeds are used (TCM 2006). Most of the secondary metabolites stimulate the blood circulation, prevent and cure cerebral edema caused by altitude sickness and have a positive effect on demential deficits (Sticher & Steinegger, 2010).

2.2.10 Witch-hazel (Hamamelis virginiana)

Leaves of witch-hazel are collected in late summer and chopped for tea preparation. Cortex of Hamamelis is used for its high amount of tannins, which amountsup to 12 %, foliage only contains up to 5 % (Sánchez-Tena et al., 2012). The bark predominantly contains hydrolysable tannins, whereas leaves mainly contain oligomeric proanthocyanidines. Flavonoids act as radical catchers and astringent (Theisen *et al.*, 2014). The interaction of all secondary metabolites creates an anti-inflammatory effect (Bäumler, 2007).

2.2.11 Dog Rose (Rosa canina)

Among others, such as several vitamins, minerals and mucus, the main component which is active in the fruit of *Rosa canina* is ascorbic acid. This combination results in an immunostimulating and antioxidative effect. Rose hips are used for tea preparations with beneficial effect on influenza (Szentmihályi et al. 2002; Larsen et al. 2003).

2.2.12 European elderberry (Sambucus nigra)

Inflorescences are more often used than the elderberries itself. The diaphoretic effect of elder blossoms tea is caused by flavonoids, which can contain up to 3.5 % (Ludwig-Müller & Gutzeit, 2014). Rutin is the dominant flavonoid which was found to attenuate the production of pro-inflammatory genes (Kwon et al. 2005).

2.2.13 Pine (Pinus sp.)

According to previous named conifer spruce, needle oil is the most common drug from this gymnosperm. The essential oil contains bornyl acetate, camphene, δ-3-carene, α- and β-phellandrene, limonene and α- and β-pinene and terpinenes (Bäumler, 2007). The weighting of the substances varies between the different pine species, secondary metabolites for instance contain up to 50% α-pinene (Sjödin et al. 2000). Essential oil is used to soothe bronchial-diseases, rheumatic disorders and muscle soreness (Bäumler, 2007).

2.2.14 Arborvitae (Thuja occidentalis)

Young shoots are harvested in May and June. Common dosage forms are tea or essential oil which contains up to 20% of monoterpenes. Typical monoterpenes are α-thujone and β-thujone which are rather toxic and cause skin irritation. Thujones will cause warts to disappear (Rose, 1999). The combination of flavonoids (besides others, mainly quercetin and kaempferol), tannins (besides others, mainly catechin and gallocatechin), lignans, polysaccharides and glycoproteins has a highly immune strengthening effect (Bäumler, 2007).

2.2.15 Laurel tree (Laurus nobilis)

Both, bay leaves and laurels are used for their medical effect. The strong taste of bay leave makes them a common spice. The medical effect is mostly based on the essential oil which occurs in both organs. Major

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constituents are 1,8-cineole, α-terpinene, sabinene and α-pinene (Dadalioglu & Evrendilek, 2004). An increased blood flow caused by the essential oil eases symptoms of rheumatism (Ciesla, 2002).

2.2.16 Olive tree (Olea europaea)

Olive leaves are characterised by secoiridoid glycoside named oleuropein, which lowers blood pressure and cholesterol content (Omar 2010; Oi-Kano et al. 2008). Oil of the olives themselves contains polyunsaturated fatty acids (Higley and Higley, 2005).

2.2.17 Common juniper (Juniperus communis)

Urinary tract diseases are traditionally treated with juniper berries (Yarnell 2002). It containsup to 70% of the monoterpenes α-pinene and β-pinene, less flavonoids and much insulin stimulate blood circulation in kidneys**.** Tannins cause an increased intestinal peristalsis. The chemical content of the berries varies a lot due to biotoc and abiotic factors. They are usually harvested in October (Bäumler 2007).

2.2.18 English walnut (Juglans regia)

Dried green walnut leaves are rich in ellagitannins (Fukuda et al. 2003). External implementation is more common than internal. They are typically applied against fungicide, skin inflammations and reduction of transpiration (Bäumler, 2007).

2.2.19 Willow (Salix sp.)

The bark (Salicis cortex) is a typical traditional source of salicin which is metabolised into salicylic acid in the human body. Additionally, tannins and flavonoids occur (Bäumler, 2007). Traditional application is against fever, headache and inflammation. In contrast to other active substances in herbal medicines, substances in willow are not “active”, however they need to be converted to express their effect (Dingermann et al. 2002).

Table 1: Overview of utilised parts of previous described European plants. List of ingredients only shows components being relevant to the pharmaceutical effect, others occur in minor amounts or lack effect on the human and are therefore not listed.

medicinal plant incl. botanical name	plant part used	prevailing active substances
European barberry *(Berberis vulgaris)*	root	alkaloids (isoquinoline and protoberberine), oxalic acid, tannins and resin
	berries	ascorbic acid, anthocyanins, caffeic acid derivatives and organic acids
Common broom *(Cytisus scoparius)*	above ground parts	quinolizidine alkaloids (mainly sparteine)
Birch *(Betula sp.)*	leaves	flavonoids (hyperoside, quercitin and myricetin), tannins and ascorbic acid
	bark	phenols (guaiacol, cresol and catechol)
Sweet chestnut (Castanea sativa)	leaves	tannins, flavonoids and triterpenes
Oak *(Quercus robur)*	bark	tannins, flavonoids (for instance quercetin) and triterpenes

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European ash *(Fraxinus excelsior)*	bark	flavonoids (mainly hydroxycoumarins), terpnenes (mainly iridoids) and tannins
	leaves	flavonoids, iridoids, tannins, triterpenes, steroids, mannitol and mucins
Alder buckthorn *(Rhamnus frangula)*	bark	phenolic compounds (mainly hydroxyanthracene derivatives)
Spruce *(Picea sp.)*	needles	bornyl acetate and borneol, limonene, camphene, β-Phellandrene, α-pinene and β-pinene, myrcene, terpene hydrocarbons, flavonoids and ascorbic acid
Ginkgo *(Ginkgo biloba)*	leaves	flavonoids (mainly proanthocyanidins, flavonolglysodides and biflavones)
Witch-hazel *(Hamamelis virginiana)*	bark	tannins (hydrolysable tannins)
	leaves	tannins (oligomeric tannins)
Dog Rose *(Rosa canina)*	fruit	ascorbic acid, vitamins, minerals and mucus
European elderberry *(Sambucus nigra)*	inflorescences	flavonoids (mainly rutin)
Pine *(Pinus sp.)*	needles	α-pinene (mainly), bornyl acetate, camphene, δ-3-carene, α- and β-phellandrene, limonene and α- and β-pinene and terpinenes
Arborvitae *(Thuja occidentalis)*	young shoots	monoterpenes (mainly α-thujone and β-thujone, flavonoids (mainly quercetin and kaempferol), tannins (mainly catechin and gallocatechin), lignans, polysaccharides and glycoproteins
Laurel tree *(Laurus nobilis)*	leaves	monoterpenes (1,8-cineole, α-terpinene, sabinene and α-pinene)
Olive tree *(Olea europaea)*	leaves	secoiridoid glycoside (oleuropein)
	fruit	polyunsaturated fatty acids
Common juniper *(Juniperus communis)*	fruit	monoterpenes (α-pinene and β-pinene), flavonoids, insulin and tannins
English walnut *(Juglans regia)*	leaves	ellagitannins
Willow *(Salix sp.)*	bark	salicin, tannins and flavonoids

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3 Product development and legal framework

3.1 Definition of herbal medicine / Phytopharmaceuticals

Around 1934 Henri Lecler characterised the term phytotherapy as a part of conventional medicine for the first time. The French doctor composed the "Précis de phytothérapie" (handbook of phytotherapy) in which he already distinguished between scientifically oriented modern alternative medicine and traditional herbal medicine (Capasso et al., 2003). The role of phytotherapy became so important, that even notable universities teach this field. In Berlin, Professor Rudolf Fritz Weiß (1895-1991) brought herbal medicine to an entirely new scientific level (Weiß, 2001).

In general a definition of phytopharmaceuticals dies currently now exist (Wichtl et al., 2004). However, food supplements containing herbal ingredients are defined as foods and do not underlie the here described legal framework. They are also handled in form of pills, dragées, powders and other medicine like dosage forms and thereby often give false impression of being equivalent to phytopharmaceuticals. Useful terms are given in Table 2. European Food Safety Authority (EFSA) defines two different terminologies: botanicals and botanical preparations. *Botanicals* include all botanical materials (e.g. whole, fragmented or cut plants, plant parts, algae, fungi and lichens), whereas *botanical materials* include all preparations obtained from botanicals by various processes (e.g. pressing, squeezing, extraction, fractionation, distillation, concentration, drying up and fermentation) (EFSA 2009).

Table 2: Overview of useful terms and shortcuts in the thematic field of legal framework

ESCOP	European Scientific Cooperative on Phytotherapy
EMA	European Medicines Agency
EPAR	European public assessment reports
EFSA	European Food Safety Authority
WHO	World Health Organization
AMG	German Pharmaceutical Drug Law
BfArM	German Federal Institute for Drugs and Medical Devices
THMP	Traditional Herbal Medicinal Products

Since the market of herbal medicine dominates in Germany and France and is less developed in others, the need for legal frameworks differs from country to country (Capasso et al., 2003). On a federal level, new medications require inspection to prove their safety and efficiency and official authorization before a manufacturer can bring a medication onto the market. In Germany for instance the German Pharmaceutical Drug Law (AMG) defines the requirements in terms of quality, effectiveness and dubiousness. More precisely it is mainly §22 AMG that regulates herbal drug approval. Prior official approval of any medication, the BfArM has to accept the requested authorisation for approval in Germany (Bäumler, 2007). This insight into German policies should give an idea of framework on a federal level which is why other EU countries policies are not presented. Phytopharmaceuticals are subject to the identical legal framework as synthetic medications. Compared to pure synthetic substances, herbal substances are not only defined by the effect of a single chemical, but rather by the mixture and consequent interaction of those (Capasso et al., 2003). The pharmaceutical effect results from the interacting compounds which makes it difficult to just apply laws for synthetic drugs on herbal drugs.

The driving force behind successive actualisation of the legal framework on a federal level is the Council Directive 65/65/EEC of 26 January 1965 on the approximation of the laws, regulations and administrative provisions of the Member States relating to medicinal products. Only a registration was required prior to this European wide regulation. However, all pharmaceutical products on the market subsequently had to meet admission requirements until 1990. Ultimately, the harmonisation process took longer than expected. Herbal medicinal products were only of minor importance at that time (Bäumler, 2007).

Parallel to the subsequent approval of all medications, the *European Scientific Cooperative on Phytotherapy* (ESCOP) was formed. In the meantime, thirteen national expert associations merged in order to advance

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the scientific status of herbal medicinal products and to assist with the harmonisation of their regulatory status at European level. The ESCOP represents national herbal medicine and phytotherapy associations across Europe, especially in their discussions with European medicines regulators (ESCOP, 2015).

In 1993 a Europe-wide authorisation system was established and updated in 2004 (Regulation (EC) No 726/2004), offering two ways of authorisation:

- Centralised authorisation system
- Decentralised authorisation system (Shorthose, 2011).

The *European Medicines Agency* (EMA) forms the main contact point for international authorisation procedure of phytopharmaceuticals. Member states still have their own legal framework. Located in London, the EMA connect national approval authorities in consideration of their national decisions on the plant-based medicine (Bagetta, 2012).

For the centralised authorisation system an application for regulatory approval has to be submitted to the *European Medicines Agency* (EMA). This is necessary for innovative drugs. Herbal medicine in general can also be approved by the decentralised authorisation system. The centralised authorisation system is composed of a scientific approval and a separate approval for a European wide distribution. For every medicine granted a central marketing authorisation, there is a European public assessment report (EPAR) available (Shorthose, 2011).

The decentralised authorisation system which is based on mutual recognition within the EU, is the common way for a European wide distribution of phytopharmaceuticals. A competent authority of a Member State composes an assessment report. In addition the submitter decides in which member states the medication should be distributed. Based on the mutual recognition, the member states accept the assessment report and there is no need for independent review in customer countries (Shorthose, 2011). If countries fail to reach agreement through decentralised authorisation, a final centralised decision will be taken. This more complex procedure might question and even deny preceding first assessment of the country of origin (Bäumler, 2007).

Directive 2004/24/EC and 2001/83/EC facilitate the market access for herbal medicinal products. With a traditional background and present bibliographical or expert evidence, these products were able to skip complex authorisation requirements that came along with the harmonisation of European and national law (Shorthose, 2011). If a product can be placed in one of the three groups shown in info box 1, clinical trials are not necessary. Phytopharmaceuticals often lack clinical trials and testing due to their traditional transmitted acceptance of efficiency.

Products can be placed on the market based with the criterion of being a traditional herbal medicinal product (THMP) or being subjected to a well-established use. A well-established use refers to an at least 10 years lasting use in the EU. Safety needs to be shown within all categories; efficiency does not (Shorthose, 2011).

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Info Box 1: Three categories in which herbal medicinal products can be placed to reach the market based on Directive 2004/24/EC.

Today under European medicines legislation, medicinal products containing herbal substances/preparations must fall within one of the following three categories to reach the market:

1. a product can be classified under **traditional medicinal use** provisions ('traditional use') accepted on the basis of sufficient safety data and plausible efficacy: the product is granted a traditional use registration (simplified registration procedure) by a Member State,
2. a product can be classified under well-established medicinal use provisions ('**well-established use**'). This is demonstrated with the provision of scientific literature establishing that the active substances of the medicinal products have been in well-established medicinal use within the Union for at least ten years, with recognised efficacy and an acceptable level of safety. As a result the product is granted a marketing authorisation usually by a Member State or by the European Medicines Agency.
3. a product can be authorised after evaluation of a marketing authorisation application consisting of only safety and efficacy data from the company's own development ('stand alone') or a combination of own studies and bibliographic data ('mixed application'). As a result the product is granted a marketing authorisation by a Member State or by the Agency via the centralised procedure if all requirements are met.

Germany implemented this directive through paragraph §25 AMG 76, which allows "Special Therapy Systems" to prove their efficiency by Commission-E monographs or ESCOP monographs. To take account of the rising worldwide demand for herbal medicine, the WHO also generates monographs on selected medicinal plants (WHO, 2009).

The legal framework development in terms of phytopharmaceuticals is still in progress, mainly promoted by the increasing demand. Placing a herbal product on the market can occur via different channels. Depending on the product characteristics, decisions have to be taken, whether the product is defined as food or medication, whether the centralised or decentralised authorisation system would make sense, whether it is classified for traditional or well-established use and besides other questions if monographs exist.

3.2 Pharmaceutical Grade

Producing a plant based product means comply with conditions concerning quality. The European law refers to national laws which in Germany is the AMG that states to ensure a consistent quality of raw material and extract manufacturing. Quality assurance of phytopharmaceuticals covers raw material, extraction agent and manufacturing process (Loew *et al.*, 1999).

First the material has to correspond with taxonomically predefined species and the quality of plant parts has to be standardised. For that reason, the material is compared with a reference, which is the quality profile of the already tested pharmaceutically effective substances. Natural variability is a disturbance. In order to meet the requirements, cultivated and wild batches are mixed up or it is even necessary to resort to dried batches of the past years (Cechinel-Filho, 2012). The cultivation process, seed quality, cultivation, watering, fertilisation, harvest, drying, storage and transportation is characterised by good agricultural and collection practices for medicinal plants (GACP) which are defined by the FAO (WHO, 2003). Date of harvest is plant specific and affects the active ingredient content tremendously. Different plant parts have different

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times of harvest (roots during dormancy in winter season, flowers right before or in bloom, bark in spring, seeds and fruits after full ripening) (Bajaj, 1994). Drying of the, if possible, unground material takes place very gently. The extraction agent of choice for extraction depends on the target substance. For alkaloids, such as amygdalin, hydrophilic substances (water/ethanol) are the best. It is necessary to distinguish between the method of maceration and percolation (Cechinel-Filho, 2012). Therefore, different botanical preparations of the same botanicals usually result in different chemical mixtures with impact on their effectiveness and security (Watzl & Leitzmann, 2005).

As mentioned before, cultivation decreases the production of secondary metabolites in plants but promotes a more homogeneous raw material at the same time. Taking advantage of the increased amount of secondary metabolites in wild products means challenging the variability of the material at the same time.

Developing an innovative pharmaceutical product based on NTFPs means to meet challenging requirements. Relaxation of the laws is one step to overcome the relatively high barriers to market entry. Regarding the raw material, it is hard to meet standards that are initially made for synthetic drugs. Creation of exemption clauses turned out to be a slow process since the pan-European need focuses on only a few member states. Supporting the market for plant-based medicines requires a successive detach from current European legal framework. Regarding the sum of published directives adjusting the handling of herbal medicinal products, it appears to be easier to create a legal framework independent of what is mandatory for synthetic drugs.

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4 Amygdalin in black cherry (*Prunus serotina*) – An innovative and promising NTFP?

Conversations with Waldmärker Regional Stakeholder Group about unused plant species occurring in high amounts lead to Black Cherry (*Prunus serotina*). Its special chemical composition prevents game browsing which is one reason for facilitating distribution. At the same time this substance, namely amygdalin is the focus of recent publications where amygdalin has been shown to block the growth of bladder cancer cells in vitro (Makarević et al., 2014a; Makarević et al., 2014b). This is not the first time amygdalin, also known as laetrile, has become popular as an alternative cancer treatment. Laetrile is a patented drug which originates from the natural substance amygdalin. Kanematsu Sugiura already published papers concerning the effect on cancer of this substance in the 1970s (Hutchison, 1980).

Amygdalin is present in leaves, seeds and bark of *Prunus serotina*, popularly known as black cherry (Santos Pimenta, Lúcia P et al., 2014). If amygdalin might gain popularity due to recent research, large wild populations of *Prunus serotina* in German forests are considered to be a reliable source.

Natural products are an important source of new pharmacophores, the pharmacologically active part of a molecule. For a rational approach it is necessary to use an efficient system for detection/fingerprinting. So far, only 6 to 15 % of higher plant species have gone through a systematic study of active ingredients (Balandrin et al., 1993; Fabricant & Farnsworth, 2001).

4.1 Amygdalin

Amygdalin occurs in kernels of fruits from Rosaceae species, predominantly in apricot (*Prunus armeniaca*), apple (*Malus domestica*) and almond (*Prunus dulcis*). Apricot kernels were used as a source for amygdalin in TCM for recovering from cancer (Song & Xu, 2014). An intravenous injection of it got patented in 1920, namely laetrile (Milazzo et al., 2007).

In the early 1970s billions of research dollars were used to fight cancer in the United States of America, the so called “War on Cancer” was declared by President Nixon (Sporn, 1996). Dr. Kanematsu Sugiuras research group from Memorial Sloan Kettering Cancer Center was responsible for the evaluation of the substance laetrile. Working with cancerous mice, the group found that more than 70% of the mice did not develop metastatic carcinoma if treated with laetrile/amygdalin. He wrote a book supporting the benefit of laetrile after stopping to work for the institute. Regarding the “Laetrile controversy” one speaks of cover-up on the one side and not successful repetitions carried out by other scientists on the other. Till this day, both parties insist on their findings. One considers laetrile a natural cure of cancer on the one side; on the other, opponents warn that it is ineffective and toxic. Neither opinion is scientifically proven on a large scale (Milazzo et al., 2007; Moertel et al., 1982; Newell & Ellison, 1980).

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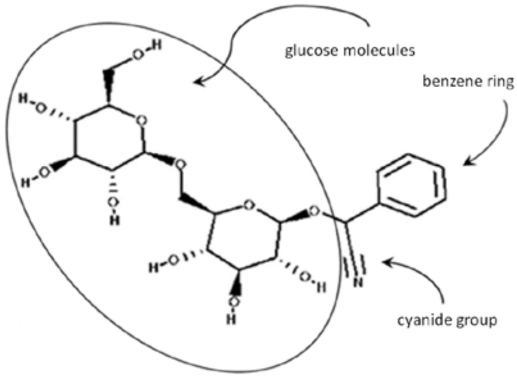

Figure 2: Chemical structure of amygdalin (Song & Xu, 2014), composed of two glucose molecules, cyanide group and benzene ring. Enzymes (β-glucosidases and hydroxynitrile lyases) and subsequent hydrolysis split off hydrogen cyanide (H–C≡N) under the presence of water (Bennett and Wallsgrove, 1994).

In 1977 the U.S. Food and Drug Administration (FDA) claimed laetrile to be toxic, since it contains cyanide. However, this cyanide is not "free" and therefore laetrile itself is not toxic. Being exposed to enzymes, hydrogen cyanide is released (Figure 2) (Song & Xu, 2014).

The following paragraph describes how amygdalin/laetrile is processed in the human body according to supporters of amygdalin/laetrile. It is known that only carcinogenic cells contain β-glucosidases. Exclusively being split off in there, the toxic effect of cyanide and benzaldehyde would only affect cancer cells. Since plants containing amygdalin usually also contain required enzymes to release the toxic effect, consumption in general implies consumption of both – amygdalin and decomposing enzymes. Apparently, healthy human cells contain rhodanese, an enzyme which converts cyanide into thiocyanate. Thiocyanate is supposed to have a beneficial effect on human health. "Free" benzaldehyde is converted into benzoic acid, which is known for its local anaesthetic effect (Griffin, 1997; Hutchison, 1980; Makarević et al., 2014a; Makarević et al., 2014b; Price and Price, 1978).

Those people holding a contrary opinion claim mechanism of selective toxicity to be ineffecive and cyanide poisining to be an unavoidable consequence (Ellison et al., 1978; Moertel et al., 1982). After FDA banned it, application also decreased in Germany since professional journals reflected this opinion (Drug Commission of the German Medical Association, 1978). However, in 2007 the Higher Administrative Court in Hanover permitted a pharmacist to sell amygdalin based on a toxicological assessment proving its non-toxicity (Lower Saxony Higher Administrative Court, 2007).

Being stored in the vacuole as an inactive glycoside, the actual effect of the secondary metabolite only appears by destruction of the cell. Exclusively the enzymatic split off by β-glucosidases and hydroxynitrile lyases enables the bioactive effect (Halkier & Gershenzon, 2006). Since enzymes are stored separately, compartmentalization prevents premature detonation of a "cyanide bomb" in seeds (Poulton and Li, 1994).

4.2 Black cherry (*Prunus serotina*)

Black cherry is originally from North America, where they reach a height of up to 35 m. Developing a shrubby habitus under unfavourable conditions, the tree did not meet the expectations for what it was introduced to Europe. Whereas in the home country the tree provides valuable timber, *Prunus serotina* it turned out to be a plague, especially in German forests (Schreier et al., 2005). The dominance in the forests is due to their high amygdalin content (Bennett and Wallsgrove, 1994).

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Figure 3: Black cherry (Prunus serotina): Drawing of inflorescence, leaves and fruits (Guimpel & Friedrich, 1825) (left), ripening cherries on campus of University of Hamburg (Verena Becker) (right).

4.3 Chemical evaluation of Black cherries collected from the wild

In August 2014 fruits of *Prunus serotina* were collected from seven different locations in Northern Germany, namely the Waldmärker region (samples A to D) and Hamburg (samples E to G). Fruits usually fall shortly after ripening; additionally perfect ripeness varies even between fruits near each other (Figure 3). Both aspects complicate the picking process. Clusters of cherries were cut off by telescopic scissors and shaking indicated ripe cherries, which fell off easily. An average amount of 250g was collected per individual.

The intention of this analysis is the determination of the average amygdalin content of the fleshy part and the pit. The fleshy part sample includes exocarp and mesocarp, whereas the pit consists of endocarp and seed. Fruits were stored at -20 °C. Exocarp and mesocarp were separated from the pit by using a common razorblade. Both parts were homogenised for high performance liquid chromatography (HPLC).

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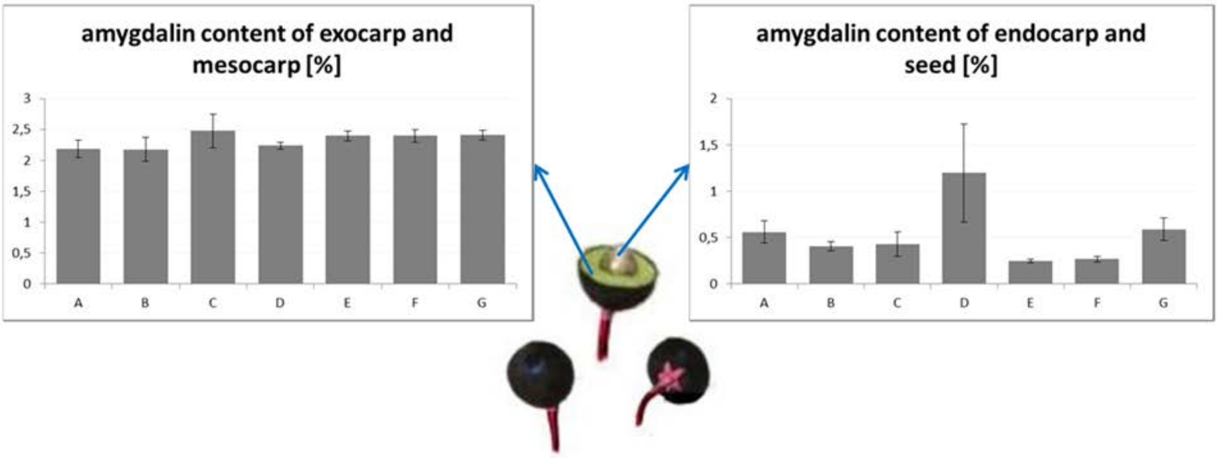

Figure 4: Amygdalin content of fruit flesh and pit. Sample A to D originate from the Uelzen region (Waldmärker), whereas sample E to G originate from Hamburg region (Drawing according to Guimpel & Friedrich, 1825). Analysis was done in the Hamburg School of Food Science by P. Werner.

Black cherries exocarp and mesocarp of *Prunus serotina* contain an average of 2.33 ± 0.12 % amygdalin, whereas endocarp and seed contain an average of 0.53 ± 0.32 %. Fruits of the Siberian apricot tree were so far found to have the highest amygdalin content. The pulp of bitter apricot (Siberian apricot, *Armeniaca sibirica* Lam.) shows a content of 3.43 % in the ripe state, whereas the seeds contain 5.1% (Zhao, 2012). Zhao removed the seed-coat (endocarp) and solely looked at the seed, which led to a considerably higher content compared to the analysed endocarp and seed mixture of *Prunus serotina*.

Based on recent research, *Prunus serotina* has the potential of an innovative NTFP. As mentioned above, amygdalin has a proven effect on cancer cells. Due to the long-time ban on using it by law and the public perception of this product, it might not be easy to make it a reliable product. However, also bitter apricot kernels have their market in Germany due to their amygdalin content (including advisory limits on levels of consumption) (CBI Market information data base 2014). Similar to bitter apricot kernels, *Prunus serotina* is also very nutritious. Positioning of a NTFP based on chemical substances in the market requires a definition whether the product is a food supplement or pharmaceutical product. Based on this, different laws apply in order to protect consumers from health hazards and deception.

In order to avoid the release of cyanide, black cherries should not be consumed as a whole. Therefore, the fruit flesh and pit should be seen as individual products. Huge variations cannot be observed between the different origins of the samples, which are beneficial for a homogenous raw material. However, it is likely that variations still exceed framework for a standardised raw material. An exclusive utilisation of NTFPs will always be limited by that. Current used wild herbs are usually blended with cultivated herbs to meet requirements; cultivated *Prunus serotina* involves plantations which are not common.

The past of amygdalin is marked by difficulties of getting onto a market. Ernst T. Krebs claimed amygdalin to be a vitamin in order to classify it as nutritional supplement, instead of a medication and to thereby escape the federal legislation regarding the marketing of drugs (Lerner 1981). Times have changed; a careful product development of wild black cherries might provide a natural product whereby recent cancer research results are applied.

Growing interest and increasing use of complementary medicine over the last decades provide a suitable foundation for innovative products. Seen as an addition to conventional medicine, efficacy and safety also

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need to be guaranteed. In general, challenges are related to regulatory status, assessment of safety and efficacy, quality control, safety monitoring and lack of knowledge about phytopharmaceuticals within drug regulatory authorities (WHO 2005). Toxico-pharmacological investigations represent minor obstacles since costs are low compared to clinical trials and serious side effects rarely arise. A clinical trial is the most expensive step of product development for the producer (Länger & Schiller 2004). Costs vary between 50 000 € and 50 million € on the German market (Pharma Fakten 2015). Having in mind that NTFPs are usually traded by small enterprises emphasizes the hurdles promising chemical substances face to become a phytopharmaceutical.

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