Chemistry Research and Applications

Supercritical Carbon Dioxide

Functions and Applications

Evie P. Hayden
Editor

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SUPERCRITICAL CARBON DIOXIDE

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PREFACE

Supercritical Carbon Dioxide: Functions and Applications presents a constructive overview on the use of supercritical carbon dioxide as an alternative solvent to obtain natural products, instead of using conventional organic solvents. The overview includes the fundamentals, industrial applications, and main experimental findings based on recent studies about supercritical extraction using carbon dioxide.

Next, the impregnation of polymer materials with two different ketones with known activity against the main pests of stored products (thymoquinone and R-(+)-pulegone) is presented, and the effect of the process variables on ketone loading and the final activity of the impregnated materials is discussed.

The authors go on to evaluate the effect of temperature (T: 41□69°C) and CO2 density (D: 843□957 kg/m3) on the extraction yield of oil and bioactive compounds of N. gaditana using supercritical CO2, a technology that allows for the selective extraction of compounds of interest by varying the pressure and temperature conditions, producing natural extracts without the use of liquid organic solvents.

Hydrophobic modifying coatings on textile materials made of polyethylene terephthalate were obtained by precipitating a low molecular weight fraction of ultrafine polytetrafluoroethylene. The modifier application conditions are also defined.

The closing chapter provides an overview on the principal applications related to the supercritical fluid extraction of active compounds from tobacco and tobacco waste, emphasizing the influence of the most important processing parameters on the extraction yield.

Chapter 1 - This chapter presents a constructive overview of using supercritical carbon dioxide as an alternative solvent to obtain natural products instead of using conventional organic solvents. The chapter includes fundamentals, industrial applications, and the main experimental findings based on recent studies about supercritical extraction using carbon dioxide. Initially, fundamental aspects of carbon dioxide properties are discussed in order to promote a better understanding of this environmentally friendly solvent called “green solvent” and to highlight its widest potential applications. Thereafter, the main technologies for the extraction of natural products using supercritical carbon dioxide are presented. The large-scale commercial plants using supercritical carbon dioxide extraction, such as coffee and tea decaffeination in the food industry and natural pesticide extraction in the agricultural area, are also presented and discussed. The overview is based on results reported by scientific studies published in the last ten years (2009-2019). Based on patents, the reality and expectations of extractions using supercritical carbon dioxide are presented. When evaluating the expectations for improving supercritical technology to obtain natural products by extraction of target compounds from vegetal matrices and microorganisms, some recent researches that achieved promising results are also highlighted. At the end of the chapter, future outlooks on the subject are provided as well as the major technological advantages of using this attractive solvent.

Chapter 2 - Terpene ketones are botanical compounds involved in natural defense mechanisms of numerous plant species, making part of a group of substances that play an important role protecting the plant from pest attack, with specific activities against several microorganisms and insects. These biodegradable compounds generally show a high selectivity with low toxicity for mammals, fish, and birds, and therefore they could be very useful as biopesticides in agroindustrial pest management, to protect crops, seeds, and related food products with low environmental risks.

Notwithstanding these advantages, terpene ketones are highly volatile, thermolabile and sensitive to UV radiation, which constitutes a limitation for their use as biopesticides. Besides, they are normally extracted from vegetable matrices as a mixture of various volatile compounds known as *essential oil*, and they must be further processed in order to obtain a purified extract with the desired specific activity. Consequently, some technological solutions are needed before their application could be achieved at a great scale. In this sense, supercritical fluid technology appears as an innovative tool to overcome these limitations.

On one hand, supercritical fluid extraction using CO_2 (pure or mixed with cosolvents) is a well-known technology with interesting advantages over other extraction techniques for the obtention of essential oils and/or other extracts from plants, as well as for the valorization of agronomical residues. This technique yields high-quality extracts, since the raw materials are not exposed to high temperature and other degrading agents (such as oxygen, radiation, etc.), and has been applied to a great number of plants and vegetable materials for obtaining aromas, nutraceuticals, bioactive compounds and other natural compounds of interest. In addition, the different solubility behavior of polar and nonpolar substances in supercritical CO_2 ($scCO_2$) allows the fractionation of mixtures (such as essential oils) and the purification of target compounds or families. In particular, ketone-rich essential oils can be treated with $scCO_2$ in order to remove the more volatile nonpolar compounds and increase or purify the fraction of ketones. Two cases of interest are presented and discussed in this chapter: i) the purification of tagetenones from *Tagetes minuta* essential oil, and ii) the recovery of piperitenone from dementholized peppermint oil. The main interest of these α,β-unsaturated ketones is based on their potential use as biopesticides and precursors for chemical synthesis.

On the other hand, $scCO_2$ is also a suitable solvent for the incorporation of low molecular weight compounds into polymer matrices. In this sense, the supercritical impregnation of biopesticides into commercial polymer materials appears as an innovative and environmentally friendly tool to develop food active packaging and/or gradual release devices. In this chapter, the impregnation of polymer materials with two different ketones with known activity against the main pest of stored products (thymoquinone and *R*-(+)-pulegone) is presented, and the effect of the process variables on ketone loading and the final activity of the impregnated materials is discussed.

Overall, supercritical fluid technology is proposed as a promising tool to develop environmentally friendly processes for encouraging the use of terpene ketones as biopesticides at a commercial scale.

Chapter 3 - *Nannochloropsis gaditana* is a microalga with a great capacity to accumulate oils and a high content of bioactive compounds. The object of this work was to evaluate the effect of temperature (*T*: 41–69°C) and CO_2 density (*D*: 843–957 kg/m^3) on the extraction yield of oil and bioactive compounds from *N. gaditana* using supercritical CO_2, a technology that allows the selective extraction of compounds of interest by varying the pressure and temperature conditions, producing natural extracts without the use of liquid organic solvents. A response surface design was used to evaluate the effects of *T* and *D*. Oil extraction yield ranged from 46.3 to 113.4 g/kg dry substrate (d.s.) (2.5-fold), while sterol extraction yield ranged from 0.90 to 6.71 g/kg d.s. (7.5-fold), carotenoid extraction yield ranged from 1.48 to 8.72 g/kg d.s. (5.9-fold), and chlorophyll extraction yield ranged from 48.12 to 329.33 mg/kg d.s. (6.8-fold). Cumulative extraction curves were modeled using Peleg's kinetic model. The recovery of oil and compounds was favored by high temperature and CO_2 density conditions. Oil extraction was accompanied by the co-extraction of sterols, corroborated by a positive correlation ($r < 0.953$; $p < 0.01$) between them. Therefore the conditions selected (69°C and 957 kg/m^3, 63.7 MPa) can be recommended for the recovery of microalgae oil enriched in bioactive compounds, which could be used in the development of functional foods.

Chapter 4 - Supercritical (SC) carbon dioxide (CO_2) is used for textile chemistry processes. In the SC state, CO_2 becomes an excellent solvent for hydrophobic substances. There are a lot of hydrophobic objects in textile chemistry. The authors' work is devoted to the study of hydrophobic modifying coatings on textile materials made of polyethylene terephthalate

(PET), which were obtained by precipitating a low molecular weight fraction of ultrafine polytetrafluoroethylene. The modifier application conditions are defined. The influence of the processing conditions of PET of a fibrous material in SC CO_2 environment on the localization of PET cyclic oligomers on the surface of fibers is considered. The composition and morphology of coatings, hydrophobic, consumer and operational characteristics of new hydrophobic materials obtained were studied.

Chapter 5 - In the past few decades, Supercritical Fluid Extraction (SFE) using CO_2 as a solvent has gained wide acceptance as an alternative technique to conventional solvent extractions for separation of active compounds from different plant materials including tobacco, as a most produced non-food crop in the world. Tobacco contains more than 4000 compounds, together with particles and gases where a large part of them are delivered during smoking. The complex chemical composition is an important factor in valuing tobacco as an interesting extraction material. Tobacco waste, such as agricultural and industrial waste (scrap, dust, midrib) have similar chemical composition as tobacco leaves because they are derived directly during processing of tobacco. At the same time, tobacco waste can represent the potential, highly valuable and cheap material, rich in some bioactive compounds. SFE have been already implemented in tobacco processing industry for removing nicotine and producing low nicotine tobacco, but recently some other application for extraction of solanesol and aroma compounds were also developed.

This chapter provides an overview on the principal applications related to SFE of active compounds from tobacco and tobacco waste emphasizing the influence of the most important processing parameters (pressure, temperature, time, solvent flow rate, particle size and co-solvents) on the extraction yield of the most important compounds and their possible application.

The application of SFE in separation of active compounds from tobacco and tobacco related materials, represents a new promising and environmentally friendly technique for the production of biologically active compounds, especially nicotine, solanesol and volatile compounds which could be further incorporated into new high-value products.

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Chapter 1

SUPERCRITICAL CARBON DIOXIDE USED FOR NATURAL PRODUCT EXTRACTION

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ABSTRACT

This chapter presents a constructive overview of using supercritical carbon dioxide as an alternative solvent to obtain natural products instead of using conventional organic solvents. The chapter includes fundamentals, industrial applications, and the main experimental findings based on recent studies about supercritical extraction using carbon dioxide. Initially, fundamental aspects of carbon dioxide properties are discussed in order to promote a better understanding of this environmentally friendly solvent called "green solvent" and to highlight its widest potential applications. Thereafter, the main technologies for the

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Chapter 5

OVERVIEW ON THE APPLICATION OF SUPERCRITICAL CO_2 EXTRACTION OF ACTIVE COMPOUNDS FROM TOBACCO AND TOBACCO WASTE

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ABSTRACT

In the past few decades, Supercritical Fluid Extraction (SFE) using CO_2 as a solvent has gained wide acceptance as an alternative technique to conventional solvent extractions for separation of active compounds from different plant materials including tobacco, as a most produced non-food crop in the world. Tobacco contains more than 4000 compounds, together with particles and gases where a large part of them are delivered

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during smoking. The complex chemical composition is an important factor in valuing tobacco as an interesting extraction material. Tobacco waste, such as agricultural and industrial waste (scrap, dust, midrib) have similar chemical composition as tobacco leaves because they are derived directly during processing of tobacco. At the same time, tobacco waste can represent the potential, highly valuable and cheap material, rich in some bioactive compounds. SFE have been already implemented in tobacco processing industry for removing nicotine and producing low nicotine tobacco, but recently some other application for extraction of solanesol and aroma compounds were also developed.

This chapter provides an overview on the principal applications related to SFE of active compounds from tobacco and tobacco waste emphasizing the influence of the most important processing parameters (pressure, temperature, time, solvent flow rate, particle size and co-solvents) on the extraction yield of the most important compounds and their possible application.

The application of SFE in separation of active compounds from tobacco and tobacco related materials, represents a new promising and environmentally friendly technique for the production of biologically active compounds, especially nicotine, solanesol and volatile compounds which could be further incorporated into new high-value products.

Keywords: tobacco, waste, supercritical fluid extraction, active compounds

1. INTRODUCTION

Tobacco usage dates from the 16th century, and it has been reported to be used as a medicine, for relaxation and in religious ceremonies. In North American society, tobacco was exclusively used as a medicine because of its mild analgesic and antiseptic properties and it was recommended for tooth pain or for healing open wounds. The use of tobacco from the very beginning as a medicine has expanded in recent times. Tobacco was inhaled, chewed, eaten, drunk, smoked, smeared on the body, used in eye drops and beverages, and for the first time was consumed by smoking in North America. The massive commercialization of tobacco began in the 19th century with the establishment of first tobacco industries. Since then no other plant has been able to replace tobacco. It is grown all over the world and its market is constantly growing and developing.

Around 4000 substances were reported to be contained in tobacco and 1000 of them are produced during smoking (Tayoub et al., 2015). During different tobacco handling processes, such as maturing, drying, fermenting, processing and storage, chemical composition is changing as well. Moreover, chemical composition depends on species, on cultivation, climatic area and many other factors (Banožić et al., 2018). For example, during the leaf drying, amount of starch decreases while at the same time, amount of reducing sugars increases. Amounts of polyphenols and carbohydrates are subjected to changes, and usually decreased during drying (Bhisey, 2012). Different groups of compounds are contained in tobacco, namely alkaloids (Shen et al., 2006), terpenoids and essential oils (Cvetanovska et al., 2017), aroma compounds (Popova et al., 2015; Popova et al., 2019) limonene, indole, pyridine (Gozan et al.,2014), fatty alcohols and phytosterols (Liu et al., 2010), proteins (Rincón et al., 1998), phenolic compounds (Chen et al., 2007; Docheva et al., 2014) and solanesol (Wang et al., 2018; Hu et al., 2015).

Tobacco and tobacco related materials are considered to be a significant source of alkaloids. Tobacco leaf contain alkaloids in amount of about 3.12%. Tobacco alkaloids are composed of about 95% nicotine and about 5% other alkaloids. Less contained alkaloids in tobacco leaves are nornicotin, anatabine, anabasine, and myosmin (Shen et al., 2006), muscarin, atropine, quinine, morphine, strychnine (Vieira et al., 2010). Beside nicotine, which has been shown to be responsible for human addiction of tobacco, other alkaloids also possess significant physiological activities (Vieira et al., 2010). Secondary metabolites such as phenolic compounds and alkaloids, and even some primary metabolites such as carbohydrates contribute in creating of tobacco specific aroma (Talhout et al., 2006; Cai et al., 2015).

1.1. Tobacco Waste

During processing of tobacco, a large amount of waste is created. The process of generating tobacco waste can be divided into three stages:

1) Waste from tobacco growing and drying - agricultural waste;
2) Waste from the production of tobacco products - industrial waste;
3) Post-consumption waste - consumer waste (Novotny et al., 2015).

There is no general agreement on definition of tobacco industry waste. Usually, it is been reported as a solid waste, generates during leaf processing, and described as low-quality tobacco or tobacco dust (Chen et al., 2007). Briški et al. (2003) reported that tobacco waste usually contain small leaf particles, unsuitable for further processing. In their study, Wang et al. (2007) reported that more than 20% of tobacco material is being discarded as tobacco waste. Tobacco leaves processing generates three fraction of tobacco waste, with differences in granulation, generation place during processing, and moisture content. During leaf processing different techniques are applied in order to achieve appropriate chemical, physical, and organoleptic properties of final product. During most stages, waste is generated. Processing of tobacco leaves generates 3 type of waste, namely scrap, midrib and dust. Midrib is a part of tobacco leaf, extended from the stalk.

Tobacco processing requires removing of midrib because it causes holes in final products, and changes in flavor, characteristic as well (Zielke et al., 1997). Scrap represents smaller broken pieces of tobacco leaf, generated during the processing of tobacco, which are not appropriate for further processing. Dust represents the smallest fine particles, which are too small for any other utilization. Depending of their quality, granulation and chemical composition, they are returned to process or disposed. Structure and chemical composition of disposed waste depends on tobacco variety, classes of tobacco and harvest time. To be used for production of reconstituted tobacco, tobacco waste should contain less than 12% of moisture.

2. Extraction of Active Compounds from Tobacco and Tobacco Waste

The great interest in bioactive components, as well as on the techniques of their production and their impact on the human body, has resulted with the massive searching of new resources of these compounds. Bioactive compounds are found in plants in very small quantities, and their isolation requires extraction processes, high solvent and energy consumption, and complex purification processes (Cvjetko Bubalo et al., 2015). Alternative sources of these components, such as industrial waste, have proven to be more economically viable, but also more environmentally friendly. Therefore, waste is used in a new or at least more efficient way.

As a result of the large differences between different classes of target bioactive compounds, their structures and natural sources, their physical and chemical properties are also variable. Therefore, it is very important to find the most effective method for extracting the targeted bioactive compounds from the selected by-products and then to optimize the extraction process itself. Conventional Extraction Techniques (CE) still use harmful organic solvents. So more recently, innovative green extraction techniques are being used for better quality of the extract itself, but also for consumption of resources (time, solvent, and energy). Most commonly used innovative extraction techniques for separation of bioactive components from by-products, are Supercritical Fluid Extraction (SFE), Subcritical Water Extraction (SWE), Ultrasonic Assisted Extraction (UAE) and Microwave Assisted Extraction (MAE). Each of these extraction techniques has its advantages, so it is important to examine all the techniques and process parameters of each extraction technique and to compare them with conventional extraction methods in order to get a real insight into the effect of each method on the yield and content of bioactive compounds in the obtained extracts.

Bioactive compounds have diverse biological activities and they are being reported in the prevention and treatment of various diseases. They are widespread in plants and have no nutritional value, with exception for some polysaccharides and proteins, who beside nutritional as primary function, possesses some bioactivities. In plants metabolism, they have a function as growth promoters or they are being produced as a response to various biotic and abiotic stresses. So far, several studies on bioactive components in tobacco waste have been published using UAE (Banožić et al., 2019) (Wang et al., 2010), SWE (Jokić et al., 2019) and MAE (Chen et al., 2007b).

2.1. SFE of Active Compounds from Tobacco and Tobacco Waste

The discovery of supercritical solvents in the world is gradually replacing toxic and environmentally harmful organic solvents. SFE is an innovative technology and is an excellent alternative to conventional organic solvent extraction processes. This is due to the numerous advantages of a supercritical solvent such as better diffusion, lower viscosity and lower surface tension, which allows it to penetrate better into the material from which the desired substance is extracted. Also, this process enables high selectivity and control of the dissolving capacity of the desired component in supercritical fluid by changing the pressure and temperature and simply removing the solvent from the extract. Furthermore, carbon dioxide (CO_2) is generally recognized as a safe solvent (GRAS), considered completely safe for use in the production and processing, which leaves no trace in final product. This energy-efficient process belongs to "clean technology" because there are no secondary products harmful to the environment (Brunner, 2005; Wang and Weller, 2006; Reverchon and De Marco, 2006; Abbas et al., 2008; Jokić, 2011; Cvjetko Bubalo et al., 2015).

Supercritical fluids are most often used alternative solvents in industry. Their application has been recognized as "environmentally friendly" due to their elimination of toxic solvents from processes, but easy product separation and by-products minimization as well. They are not only used in separation processes, but also in material processing, homogenization, sterilization, dispersing, biochemical reactions and chromatography. CO_2 is the most commonly used SFE solvent because of its safety, availability and a low cost. In addition, some advantages as simple regeneration of used solvent, prevented oxidation during the processes, accelerated processes have also been reported. SFE gained huge interest in the last decades and is been implemented in different separation process for extraction of phytochemical from different natural materials (Cvjetko Bubalo et al., 2015). Under supercritical conditions (temperature over 31°C and pressure over 7.28 MPa) CO_2 has high diffusivity, low viscosity and low surface tension, which allows better mass, transfer from plant cells. CO_2 soluble compounds at process conditions remain in the fluid phase; whereas, insoluble compounds precipitate and a very effective fractionation can be obtained. Moreover, once used CO_2 can be recycled and again returned and used in the process (Jokić et al., 2013).

2.2. SFE of Nicotine from Tobacco and Tobacco Waste

Most of the published research on SFE related to tobacco and tobacco waste are related for extraction of solanesol and nicotine and only some authors (Scrugli et al., 2002; Rodriguez et al., 2008) reported extraction of other compounds. Nicotine is the major tobacco alkaloid, usually found in tobacco in amounts from 0.3 to 7%, depending on the tobacco variety, cultivation conditions, processing method and other conditions. Due to its high nicotine content, tobacco waste is considered extremely hazardous and is not suitable for disposal as ordinary waste (Tayoub et al., 2015). Nicotine, on the other hand, is an extremely important compound that has antimicrobial and insecticidal properties and can also be used in the treatment of some nervous system diseases. In the plant itself, nicotine begins to form at the root of the plant, and it accumulates in the leaves. For commercial purposes, it is produced by extraction from tobacco, but it is also contained in other plants of the *Solanaceae* family, such as tomato leaves, potato leaves, but in much smaller quantities. Nicotine content is a key factor in evaluating the quality of tobacco, and apart from the variety itself, it is closely linked to soil type, climatic conditions, soil nutrition, degree of maturity or maturation of tobacco, and drying conditions.

Table 1. Studies of SFE extraction of nicotine from tobacco and tobacco waste

Material	EXTRACTION CONDTIONS				Reference
	Pressure (bar)	Time (min)	Temperature (°C)	Co-solvent	
Leaves	100	-	40	Ethanol/ 1% KOH	Scrugli et al., 2002
Leaves	137	35	100	Methanol/ M KH_2PO_4 (2:3)	Fischer and Jefferies, 1996
Leaves	260	-	70	-	Coffa et al., 2016
Tobacco waste	150-300	180-300	50-70	-	Rincón et al., 1998
Leaves	80-250	60	25-60	-	Rodriguez et al., 2008

Nicotine content is a frequent subject of medical research since its presence in the human body is associated with the formation of carcinogenic nitrosamines (Moghbel et al., 2015). In small amounts (up to 1 mg), nicotine has stimulating effects, while larger amounts (30-60 mg) can be lethal as it has acute and chronic toxicity and has a negative effect on the circulatory, respiratory, gastrointestinal and immune systems (Karačonji, 2006). On the other hand, nicotine has been shown to have positive effect in treatments of patients with dementia (White and Levin, 1999) and schizophrenia (Levin et al., 1996), dopaminergic neurons and axons (Maggio et al., 1998), and mild cognitive dysfunction (Newhouse and et al., 2012). In addition, nicotine is thought to assist in the treatment and prevention of Parkinson's and Alzheimer's disease and Tourette's syndrome.

Since nicotine content is related with tobacco addiction and other harmful effects on human health, many studies were conducted in order to minimize nicotine content in tobacco products. In the beginning they were considering solvent extraction of nicotine (Narasimha et al.1992, Millen et al., 1993), but in recent time other innovative extraction techniques are suggested to implement in tobacco processing industry for removing nicotine and producing low nicotine tobacco. Sherer and Lee (1999) claimed that reducing nicotine from tobacco in range from 90 to 95%, could significantly effect on addiction from tobacco products or help with completely cessation. There are some limitations regarded to selectivity of the process, because supercritical CO_2 extraction removes other alkaloids and waxes (Morgan, 2000) and flavoring compounds (Scrugli et al., 2002). That can results in changes in formaldehyde yields of cigarette smoke (Piade et al., 2013), which is dramatically decreased in low nicotine and denicotinied tobacco (Coffa et al., 2016). Moreover, they reported biological activity of denicotinied tobacco. SFE of tobacco leaves resulted in chemicals changes of smoke, but it did not resulted with changes in cytotoxicity and mutagenicity. Nevertheless, developing of tobacco product, that will contain reduced nicotine, but same characteristic flavor, remains challenge for tobacco industry.

SFE process of tobacco leaves for removing nicotine has been developed and patented early, in 1973. (Roselius et al., 1993), but took a long time to determine which process parameters effect on SFE of nicotine. There are several studies dealing with influence of SFE on nicotine from tobacco leaves (Table 1). All this studies suggest that SFE is more selective for nicotine than extraction with conventional solvents. In study by Fischer and Jefferies (1996) the influence of particle size, cell geometry, and packing of the extraction cell on nicotine yield using SFE were investigated. In their research particle size did not influence the extraction yield of nicotine, but on the other hand they proved that moisture content and presence of other compounds in extraction material, such as α-cellulose, can significantly affect SFE selectivity and extraction yield. Various studies proved that pressure have significant impact on nicotine yield during SFE (Rincón et al., 1998; Rodriguez et al., 2008; Karbalaie et al., 2009). Results from study by Karbalaie et al. (2009) showed that the pressure has the maximum effect (86.9%) on the nicotine SFE. Rincón et al. (1998) have published specific study, in order to optimize the extraction process of nicotine from tobacco waste. They suggested that extraction yield increases with increasing pressure, and the highest extraction yield gave temperatures between 50-60°C, and above

60°C extraction yield started to decrease. Rodriguez et al. (2008) proved that SFE performed on higher temperatures results with extracts rich in nicotine, and SFE on lower temperatures results with solanesol-rich extracts. Differences in SFE parameters influence on tobacco and tobacco waste could be explained by differences in particle structure. However, for SFE of tobacco and tobacco waste, higher pressures are preferable due to better selectivity and higher extraction yield. During the years, SFE of tobacco leaves gained significant improvements. Nevertheless, there is still space for new research, especially in the area of tobacco waste.

2.3. SFE of Solanesol from Tobacco and Tobacco Waste

Solanesol is an acyclic trisesquiterpene alcohol. Like nicotine, it can be found in all plants of the *Solanaceae* family. It is considered as an important source of isoprene units, which can be used in the chemical synthesis of quinine and vitamin K (Tang et al., 2007), as a precursor of PAHs (polynuclear aromatic hydrocarbons (Fukusaki et al., 2004). In tobacco leaves, solanesol can be found in two states, as free and/or bound in esters with palmitic, linoleic, myristic, oleic and linoleic acids (Tang et al., 2007). Content of up to 4% of the total dry leaf mass, make it as dominant tobacco terpenoid, while it is absent in other parts of the plant. The solanesol content of tobacco depends on a number of factors including tobacco type, leaf position on the stem, growth time and drying method (Tang et al., 2007). Burton et al. (1989) reported that the amount of solanesol increases in proportion to the growth of the plant itself, but also during drying and fermentation process. Both methods of solanesol production, synthesis and extraction, are complex, demanding and time-consuming processes.

For the extraction of solanesol, saponification must be carried out in order to release the solanesol bound forms since solanesol is bound in the form of a fatty acid ester. Saponification can be carried out with potassium hydroxide (Wang et al., 2018) or with sodium hydroxide (Hu et al., 2015). After saponification, free solanesol can be extracted using conventional or innovative extraction methods. Conventional solanesol extraction methods include the use of harmful solvents such as hexane. At the same time, satisfactory amounts of solanesol can be obtained using UAE (Banožić et al., 2019), MAE (Zhou et al., 2006) and SFE (Huang et al., 2008; Rodriguez et al., 2008).

Table 2. Studies of SFE extraction of solanesol from tobacco and tobacco waste

Material	EXTRACTION CONDTITIONS				Reference
	Pressure (bar)	Time (min)	Temperature (°C)	Co-solvent	
Discarded tobacco leaves	183-517	100-180	40-66.7	23% Ethanol	Huang et al., 2008
Tobacco waste	100-300	120	40-80	-	Wang et al., 2018
Leaves	200	120	45	Ethanol	Yunren et al. 1996
Leaves	350	180	50	-	Xin et al., 2006
Leaves	80-250	60	25-60	-	Rodriguez et al., 2008
Leaves	250	120	45	-	Wen-Song et al., 2007

SFE of tobacco was subject of many studies (Table 2). Rodriguez et al. (2008) used SFE of tobacco leaves for extracting solanesol, and followed by GC-MS analysis. Besides solanesol, obtained extract were characterized by high level of nicotine and presence of α-tocopherol. The highest yield of solanesol was achieved at following condition at 40°C and 150 bars and 25°C and 80 bars. Wang et al. (2018) studied influence of used pressure, temperature, solvent flow rate and materials size particles on solanesol yield. Higher extraction yield of solanesol was achieved with applying higher pressures and higher CO_2 flow rate, but lower particle size as well. Opposite, temperature did not show any significant influence on extraction yield of solanesol. Similar results were found in research published Huang et al. (2008) on tobacco leaves, where higher pressure and consequently higher CO_2 density increases solanesol yield. Optimum SFE condition for maximum crude solanesol yield was as follow, 45 °C, 38 MPa and 2.6 h. Several studies suggest lower temperatures for extracting solanesol. Xin et al. (2006) reported 98% extraction of 40.01 wt% solanesol purity applying

SFE conditions of temperature 50°C and pressure 35 MPa. It has also reported 92.1% recovery of solanesol without presenting solanesol purity applying SFE conditions of 45°C and 25 MPa for 2 h (Wen-Song et al., 2007). Generally, it can be concluded that lower temperatures are preferable for SFE of solanesol. Besides temperature, there is one factor to consider before, SFE, and that is pretreatment. Solanesol is low polar compound and has low solubility in CO_2. A pretreatment using hexane/ethanol or petroleum ether/ethanol solution is suggested for enhancing solanesol solubility in CO_2 (Wang et al., 2018). Higher ethanol concentrations are undesirable, because of saturation of CO_2 and possible formation of two phases (Hasbay-Adil et al., 2007).

2.4. SFE of Tobacco Seeds

Tobacco seed represent value part of tobacco plant, usually discarded on field as agricultural waste. On the contrast, tobacco seed contain high percentage of oil. The size of these seeds is very small, but one tobacco plant can contain thousands of seeds. The weight of 1 000 seeds is 0.06 - 0.1 g, and the hectoliter weight is about 40 - 45 kg. Although it does not belong to edible oils, physical and chemical properties of this type of oil are comparable with other vegetable oils (Giannelos et al., 2002). Several extraction techniques were applied for extraction of oil from tobacco seeds, including soxhlet extraction (Giannelos et al., 2002), extraction with diethyl ether (Usta et al., 2005), UAE (Eshetu et al., 2005) and SFE (Majdi et al., 2012).

Fatty acid composition of tobacco seed oil was found to be highly preferable. Majdi et al. (2012) performed SFE of tobacco seeds. The fatty acids composition of tobacco seed oil was dominated by linoleic acid (59.8 – 66.82%), similar to research by Stanisavljević et al. (2009) where content of linoleic acid was 70%, obtained with UAE. In this case, pressure has proven to be a major factor influencing the extraction of tobacco seed oil.

However influence of other SFE parameter should be also investigated. Since usage of this oil is very limited, some author proposed its utilization in soap or paint industry (Stanisavljević et al., 2007) or for producing biodiesel (Giannelos et al., 2002).

2.5. SFE of Other Compound from Tobacco and Tobacco Waste

Besides nicotine, and solanesol, which are the most commonly compounds in tobacco and tobacco related materials, some other compounds were also successfully extracted with SFE from tobacco (Table 3). In study of Ashraf-Khorassani et al. (2005) authors investigated SFE of tetra-acyl sucrose esters from tobacco leaves.

Tetra-acyl sucrose esters are compounds, commonly found in the cuticular waxes on leaf surface of green tobacco. They possess strong antibacterial activity, and serve as precursors of tobacco aroma. They determined that tetra-acyl sucrose esters can be extracted only using high density CO_2 (higher than 0.73 g/mL).

Table 3. Studies of SFE extraction of other compounds from tobacco and tobacco waste

Material	EXTRACTION CONDTITIONS				Targeted compounds	Reference
	Pressure (bar)	Time (min)	Temperature (°C)	Co-solvent		
Leaves	150-450	75	60-100	-	Tetra-acyl sucrose esters	Ashraf-Khorassani et al., 2005
Leaves	183-517	100-180	40-66.7	23% Ethanol	Waxes, Proteins, alkaloids	Scrugli et al., 2002
Leaves	65-150	120	23	-	Volatile compounds	Alagić et al., 2006
Leaves	100	120	40	-	Volatile compounds	Palić et al., 2002
Leaves	350	60	60	Methanol	Nitrosami nes	Prokopczyk et al. 1995

In their study Rodriguez et al. (2008) proved that SFE performed on higher temperatures results with extracts rich in nicotine, and SFE on lower temperatures results with solanesol-rich extracts. Similar results were find by Alaric et al. (2006) where higher pressure (150) give better extraction yield and wide range of extracted compounds. Some compounds were present in all tobacco SFE extracts, and there were, beside nicotine, neophytadiene, hexdecanoic acid, sclareolideand a mixture of n-alkanes. Palić et al. (2002) found neophytadiene and solanone and nonacosand as major volatile compound in Serbian varieties of tobacco. Moreover they identify some antimicrobial activity of SFE extracts against *Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa.*

Since SFE is not only used for separation of desired compounds, but it can be used for separation of undesired compounds, such as nitrosamines, Prokopczyk et al. (1995) and Song et al. (1999) successfully applied SFE for separation of tobacco specific N-Nitrosamine. Moreover, SFE was applied for extraction of some pesticides, which are compounds not native to tobacco, but usually applied during tobacco growing, such as flumetralin (Lancas et al., 1996).

2.6. Apllication of Tobacco and Tobacco Waste SFE Extracts

Nicotine extraction is an important process for the pharmaceutical industry, which has developed a wide range of non-tobacco nicotine-delivering products in recent years, such as transdermal formulations (patches), chewing gums, inhalers and even nicotine water. These products deliver nicotine into the human body in an innovative way as a substitute for smoking (Rodgman and Perfetti, 2009). Such substitute products help to quit smoking, but at the same time make it possible to avoid the harmful contents of tobacco smoke. (Charlton, 2004). The commercial use of nicotine extraction so far has been limited to tobacco products with reduced nicotine content, but in recent time many new nicotine products has been developed (Coffa et al., 2016). There are also some other possible applications related to using nicotine as insecticide or antimicrobial agent.

According to this fact, industry of producing nicotine will probably increase.

Solanesol-rich extract have potential application in cosmetic and pharmaceutical industry, since it is valuable source of isoprene units. Isoprene units are used for producing active quinones. Also, it possesses significant antioxidant, anti-inflammatory and antibacterial properties with potential application for producing drugs (Rodriguez et al., 2008). It has different biological properties, such as antioxidant (Huang et al., 2008), anticancer properties, antibacterial properties, and it can be used in the manufacture of medicine for the treatment of various diseases (Yan et al., 2015) because it acts as a cardio-stimulant in human metabolism (Rodriguez et al., 2008), while its derivatives can be used to treat cardiovascular disease, osteoporosis, acquired immunodeficiency and other diseases (Yan et al., 2015). It is industrially important, precisely because it is the starting material for many high value components, including coenzyme Q10 and vitamin K analogs (Hamamura et al., 2002). Given that coenzyme Q10 is present on the market in the form of dietary supplements to relieve migraine-induced pain (Sándor et al., 2005), a protective role in Parkinson's and other neurodegenerative diseases (Matthews et al., 1998; Shults et al., 2002; Muller et al., 2003), with a positive effect on the regulation of blood pressure and glycemia in patients with type 2 diabetes (Hodgson et al., 2002), the demand for solanesol is increasing (Lipshutz et al., 2005).

Tobacco SFE extracts rich in volatile compounds could be used in fragrance industry. For example, tobacco concrete is already used in fragrance and cosmetics industry, for production of men perfumes with woody, earthy and oriental notes (Brechbill, 2009; Nedeltcheva-Antonova et al., 2016). Tobacco, as a plant is primarily used for smoking. But in other hand it does contain a number of bioactive compounds. SFE of such compounds could provide new application of tobacco leaves or even more important, of waste that currently has no commercial value. However there are some limitations, regarded to solubility of those compounds in CO_2 and their purity in obtained extracts. Future work should focus on enhancing the quality of SFE extracts from tobacco waste, as economically, and environment-friendly source of value compounds.

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