Aromatic Plants and Bioactive Compounds

Subjects: Others

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Natural compounds obtained from different medicinal and aromatic plants have gained respect as alternative treatments to synthetic drugs, as well as raw materials for different applications (cosmetic, food and feed industries, environment protection, and many others). Based on a literature survey on dedicated databases, the content includes a critical discussion of aspects regarding classical extraction versus modern extraction techniques; possibilities to scale up (advantages and disadvantages of different extraction methods usually applied and the influence of extraction parameters); and different medicinal and aromatic plants' different applications (medical and industrial applications, as well as the potential use in nanotechnology).

medicinal plants bioactive compounds biomedical applications industrial applications

1. Introduction

Natural compounds obtained from different medicinal and aromatic plants (MAPs) have gained respect as alternative treatments, as well as raw material for different applications. Medicinal plants are a source of bioactive compounds that act as drugs in traditional treatments [1]; meanwhile, aromatic plants represent a rich source of essential oils, which can be used for their aroma and flavor [2]. MAPs are also used in cosmetics, functional food, or natural dyes production [3], thousands of species are all over the world being explored and exploited [4]. Another recent application is in the nanotechnology area, where the plant extracts' phytoconstituents act as reducing and capping agents for the reduction of metallic ions from solutions in order to obtain different metallic nanoparticles, with further biomedical or industrial applications [5] (**Figure 1**).

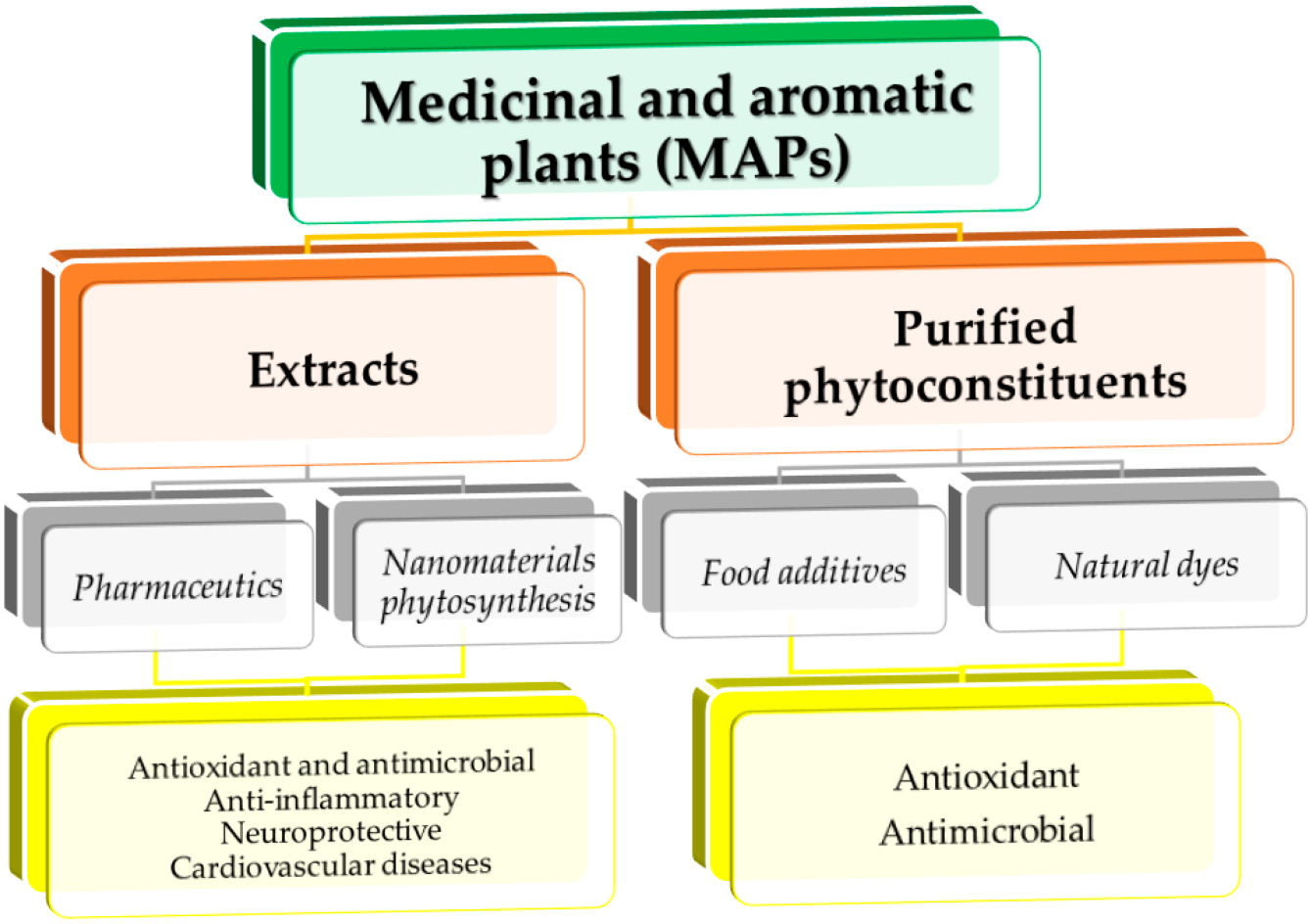

Figure 1. Some of the potential applications of medicinal and aromatic plants.

The increased population led to a higher utilization of these plants, so their residues are proportional, with a huge amount of biomass generated as by-products [6], representing a growing market in the natural-based products [7]. The general use of MAPs all over the world is not homogenic, due to different factors: (i) in developed countries, even if the demand for natural treatments is high, profits of the growers and producers remain low because of the existing intermediaries which increase the price, as well as the lack of organization and networking by the poor collectors of medicinal plants from the wild; (ii) rigorous regulations and documentations requirements; and (iii) in less developed countries, there are poor traceability mechanisms from plant to population [8].

In this context, there are many studies reporting biological effects that can be attributed to MAPs or derived products, against several diseases, such as cancer, neurological, respiratory, inflammatory, cardiovascular diseases, and many others [9][10][11][12]. Using phytoconstituents or natural-based products as complementary treatments improved the oxidative status, which is due to their activity in compensating the inefficacy of the endogenous defense systems and in the enhancement of the overall antioxidant response [13][14]. Under stress conditions, the human body produces more reactive oxygen and nitrogen species (ROS/RNS) than enzymatic and non-enzymatic antioxidants, which is conducive to cell damage and health problems [15], and biological active products have a crucial role in combating oxidative stress.

In addition to traditional medical applications of medicinal and aromatic plants, there is the possibility of using them in cosmetic products, feed or food additives and preservatives, or as a viable tool for biotechnological applications, such as the enhancement of secondary metabolites by genetic engineering [16][17][18].

2. Classical Extraction Versus Modern Extraction Techniques: Possibilities to Scale up

Classical methods were developed during the time, such as a simple approach involving only water, herbs, and energy [19]. During the optimization process, the economic costs and energy necessary for obtaining different bioactive compounds tends to decrease, leading to higher yields of target compounds. Instead of maceration, decoction, or infusion, in the past, researchers developed methods such as Soxhlet, Clevenger, Kumagawa, or Likens–Nickerson simultaneous distillation–extraction, which, in turn, are replaced in the present day with modern equipment such as microwave-assisted extraction, supercritical fluid extraction [20], or ultrasound-assisted extraction [21]. Some examples are presented in **Table 1** in order to present conditions for classical extraction versus necessary conditions for modern methods.

Table 1. Comparation of classical and modern extraction techniques for medicinal and aromatic plants.

Plant	Extraction Method	Extraction Conditions	Obtained Compounds	Extraction Yield	Reference
Allium sativum Linn.	Microwave-assisted hydro-distillation	Solvent: deionized water/diethyl ether 2:1; 100 g vegetal material; MP = 700 W; t = 30 min;	Diallyl sulfides (mono-, di-, tri-, and tetra-); Methyl allyl sulfides (di- and tri-); Vinyl dithiins	0.22%	[22]
	Ultrasound-assisted extraction	Solvent: diethyl ether (50 mL); F = 35 kHz; T = 25 °C; t = 30 min.		0.13%	
	Lickens–Nickerson apparatus	Solvent: water/diethyl ether = 1:10; 100 g. vegetal material; T = −10 °C; t = 2 h.		0.23%	
Hippophae rhamnoides L.	Solvent-free microwave-assisted extraction	400 g vegetal material atmospheric pressure; P = 400 W; T = 20–100 °C; t = 15 min.	Polyphenols with an increased yield of recovery for microwave extraction method	1147 mg GAE/g (d.w.)	[23]
	Classical extraction	Solvent: methanol 80% (50 mL); 5 g vegetal material; 8000 rpm; t = 5 min.		741.9 mg GAE/g (d.w.)	

Plant	Extraction Method	Extraction Conditions	Obtained Compounds	Extraction Yield	Reference
Matricaria chamomilla L.	Subcritical water extraction	Solvent: water (300 mL); 10 g vegetal material; P = 30, 45 and 60 bars; T = 100 °C; t = 30 min;	Polyphenols	127–3226 mg/kg	[24]
	Maceration	Solvent: water (100 mL); 2.5 g vegetal material—oven-dried chamomile at low temperatures (i.e., 40 °C); T = 100 °C; t = 120 min.	Polyphenols	19.7 ± 0.5 mg/g (d.w.)	[25]
Mentha spp.	Microwave hydro-diffusion	Solvent-free; 500 g vegetal material; MP 1 W/g; F 2.45 GHz t = 20 min.	Essential oil	0.95%	[26]
	Soxhlet extraction	Solvent: water: ethanol = 3:7 (250 mL); 1.5 g dry plant material; T = 95 °C	Polyphenols	18,381–87,024 mg GAE/kg (d.w.)	[27]
Origanum vulgare L., 1753	Supercritical extraction	CO_2 flow rate = 2.4 kg/h; 0.6 kg of vegetal material: CO_2/plant ratio = 20 kg/kg; P = 30 MPa; T = 40 °C.	Carnosic acid	3.18 ± 0.40%	[28]
	Hydro-distillation	300 g vegetal material; t = 45 min	Essential oil rich in terpenes	0.75% (d.w.)	[29]
	Maceration	Solvent: dichloromethane/ethanol = 3/1 (15 mL); 1 g vegetal material; T = 35 °C; t 3 h.	Carnosic acid, rosmarinic acid, carnosol	16.82; 0.12; 9.31 mg/g (f.w.)	[30]
Rosmarinus officinalis L.	Supercritical fluid extraction	Solvent-free CO_2 extraction; flow rate: 5 g/min; 100 g vegetal material; P = 100–300 bar; T = 40 °C; t = 3 h.	Carnosic acid, rosmarinic acid, camphor, 1,8-cineole	1.0730; 0.1242; 0.44; 0.029% (d.w.)	[31]
	Microwave-assisted extraction	Solvent: ethanol 96 %; 25 g milled leaves; Liquid/solid ratio = 6/1 (*v*/*w*); t = 7 min.	Carnosic acid, rosmarinic acid	3.3 ± 0.2 % (*w*/*v*) 3.1 ± 1.2 % (*w*/*v*)	[32]

Plant	Extraction Method	Extraction Conditions	Obtained Compounds	Extraction Yield	Reference
Salvia officinalis L.	Supercritical CO_2 extraction	Solvent-free CO2 extraction; flow rate: 1–3 kg/h; 50 g. of vegetal material; P = 15 or 20 MPa; T = 25 °C; t = 90 min.	Terpenes and phenolic compounds	0.659–5.477 % (*w/v*)	[33]
	Hydro distillation (Clevenger-type apparatus)	Solvent: water (1 L); 100 g vegetal material; t = 180 min.	Terpenes and phenolic compounds	2.0–2.1% (*v/w*)	[34]
	Maceration	Solvent: ethanol (70%)—25 mL; 5 g of vegetal material; t = 2 days;	Rosmarinic acid, carnosic acid, carnosol and methyl carnosate	n.p.	[35]
Satureja hortensis L.	Maceration	Solvent: ethanol 96% (300 mL); 10 g vegetal material; T = 22 °C; t = 7 days.	Phenolic compounds	125.34 mg GAE/g	[36]
	Soxhlet extraction	Solvent: ethanol 96% (600 mL); 75 g vegetal material; t = 8 h.		119.28 mg GAE/g	
	Microwave extraction	Solvent: ethanol 96% (100 mL); 5 g vegetal material; t = 30 min		147.21 mg GAE/g	
Thymus daenensis Celak. and *Thymus kotschyanus* Boiss. and Hohen	Hydro-distillation (Clevenger-type apparatus)	50 g vegetal material; t = 3 h.	Thymol, p-cymene, β-caryophyllene methyl carvacrol	1.2–2.4%	[37]
Thymus munbyanus Boiss. & Reut., 1852	Pressurized liquid extraction	Solvent: acetone; ethanol; water; 20 g. vegetal material; P = 45 MPa; T = 70 °C; t = 10 min	Oxygenated monoterpenoids; sesquiterpenoids and monoterpenoids	[39][40][41] 21.2 ± 0.6%	[38]

Where d.w.—dry weight; F—frequency; f.w.—fresh weight; GAE—gallic acid equivalents; MP—microwave power; n.p.—not provided by the authors; P—pressure; T—temperature; t—time.

may vary, are higher *Hippophae* osed the r code in extraction arameters siness of due to the of a color code associated to a letter, class A being the "greenest" one [41]. The selection of a suitable solvent is crucial to improve the extraction yields, and moreover, the amount of resulted waste after the extraction. Polar solvents are commonly used, such as ethanol, methanol, and isopropanol [42], but the trends in "*green chemistry*" are going toward novel solvents with less toxicity as natural deep eutectic solvents (NADES) [43]. Espino and coworkers developed and optimized ultrasound-mediated extraction for phenolic compounds from *Larrea cuneifolia* Cav. 1800, which is a medicinal plant from the *Larrea* genus used in the Argentinian folk medicine [44]. They chemometrically optimized the extraction conditions, obtaining better results than using classical solvents in terms

of resulted wastes: thus, for conventional techniques (maceration, decoction, heat reflux), wastes are in the range 1.5–2.85 penalty points for waste calculated according to the methodology previously mentioned [39][40][41], while for modern techniques, such as microwave and ultrasound-assisted extractions, wastes are in the range of 1–1.5 penalty points for waste, which are calculated according to the same protocol. These values of penalty points of the wastes offer a green certificate of class A (with a value in the range 100–90) and class B (89–80). Considering the results presented by the authors, the use of NADES and modern extraction techniques (such as ultrasound extraction) could be successfully applied for the scale-up of the procedure.

Another "*green solvent*" is carbon dioxide, which can be used as the main solvent for supercritical fluid extraction, having advantages such as non-toxicity and thermodynamic parameters, which facilitates its use in the supercritical state [45], being a suitable solvent first for non-polar molecules (lipids, terpenes, etc.), followed by more polar molecules [46]. In the case of *Salvia officinalis* L., Jokić and coworkers optimized a supercritical CO_2 extraction method for terpenes and phenolic compounds, obtaining increased yields of recovery (7.4%) by varying the utilized pressure (15 or 20 MPa) [33] in only 90 min of extraction; meanwhile, Miguel and collaborators, through hydro-distillation obtained in 180 min a decreased yield of recovery (2%) [34]. Moreover, the quality of the obtained compounds can be modified depending on the extraction method used; Ollanketo and coworkers demonstrated that pressurized hot water extraction is a highly promising alternative to conventional solid–liquid techniques, in terms of final application of the recovered compounds; the highest antioxidant activities did not correspond to the maximum recovery yields, but the antioxidant activity was highest when pressurized hot water (PHW) was used as the extracting solvent instead of the maceration method [35]. In this case, the quality of the compounds is influenced by the extraction conditions, in which an increased time and temperature lead to a decrease of biological effects of the obtained compounds. In addition, some compounds do not respond to a classical or modern solvent (such as NADES) extraction, and it is necessary to optimize an enzymatic process and break hydrogen or hydrophobic bonding, which keeps them trapped in the polysaccharide–lignin network [47].

As a pro argument for modern extraction techniques, in addition to the reduced costs and energy, there is the use of a cascade of different solvents, which is due to the existence of a complex matrix of MAPs; this approach is conducive to the recovery of a large range of bioactive compounds. This is the case of Algerian *Thymus munbyanus* Boiss. & Reut., 1852, where acetone, ethanol, and water were used in successive pressurized extractions [38]. The recuperation of the solvents, especially the toxic ones such as acetone, can be performed under vacuum conditions, removing the possibility of contamination on the environment or on the final products. In addition to oxygenated monoterpenoids, such as camphor (11.7%) and geraniol (7.5%), and sesquiterpenoids and monoterpenoids, such as (E)-nerolidol (13.7%), terpinen-4-ol (10.6%), and camphor (7.6%), researchers also obtained geranyl acetate (6.3%) and β-terpinyl acetate (5.1%), caryophyllene oxide (5.1%) and borneol (5.6%), respectively β-terpinyl acetate (4.8%) and linalool (4%).

A proper balance in choosing the methods and setting operational parameters could lead to an optimized process, obtaining different compounds from a plant matrix, which in other conditions would be damaged or could not be obtained [48]. The structure of target molecules can influence their solubility at different conditions of high pressure; in extreme conditions, interactions and aggregations or even their re-adsorption are possible. Using moderate

conditions such as medium pressures or temperatures automatically can result in lower costs and energies, which is beneficial for all the production and processing chain. Moreover, for modern extraction methods, for which it is not necessary to use organic or toxic solvents, the obtained bioactive compounds could achieve, in certain conditions, a “green characteristic” and can be used in further applications such as the design of foods with improved functionality or medical care.

Modern extraction methods have attracted a great amount of interest in the last few years, especially due to their scale-up possibilities and their ability to provide superior quality extracts with economic benefits; a scientific and analytical approach must be conducted for this step. The classical extraction method can be also scaled up, but factors such as instrumentation, batch/flow process, kinetics, economics, energy consumption, and amounts of wastes tilt the balance toward the scale up of non-conventional extraction techniques, such as microwaves or ultrasonic-assisted, supercritical fluid, negative cavitation, pressurized fluid, etc. [49]. In some cases, the adequate parameters for lab scale can be used in scale-up process [50], but in other cases, maintaining the same conditions can led to a decreased recovery yield when the scaled-up method is applied [51]. In the optimization process, there must be a balance between the parameters, and according to Belwal and coworkers, every method must prove its maturity level through technology readiness levels (TRL) [49].

3. The Influence of Extraction Conditions

For each method used as an extraction technique, optimization of the parameters is mandatory. The reaction parameters that can influence the extraction process are the used solvent, temperature, ratio of vegetal material/amount of solvent, pH, extraction time, and factors related to the raw material matrix [52].

According to the experiments performed by different authors, the most suitable solvents for bioactive compounds extraction are water for anthocyanins, phenolic acid, saponins, terpenoids recovery [53][54][55][56], and alcohols such as methanol or ethanol, alone or as mixtures, for anthocyanins, phenolic acids, flavonoids, tannins, saponins, or terpenoids recovery [57][58]. Alcohols have the property of increasing cell permeability by affecting the phospholipid bilayer of the membrane, permitting a good transfer of bioactive compounds into the solvent. In addition, the water/alcohol mixtures permit a good recovery yield, especially for phenolic compounds, which have a good solubility, due to the alcohol presence (**Figure 2**).

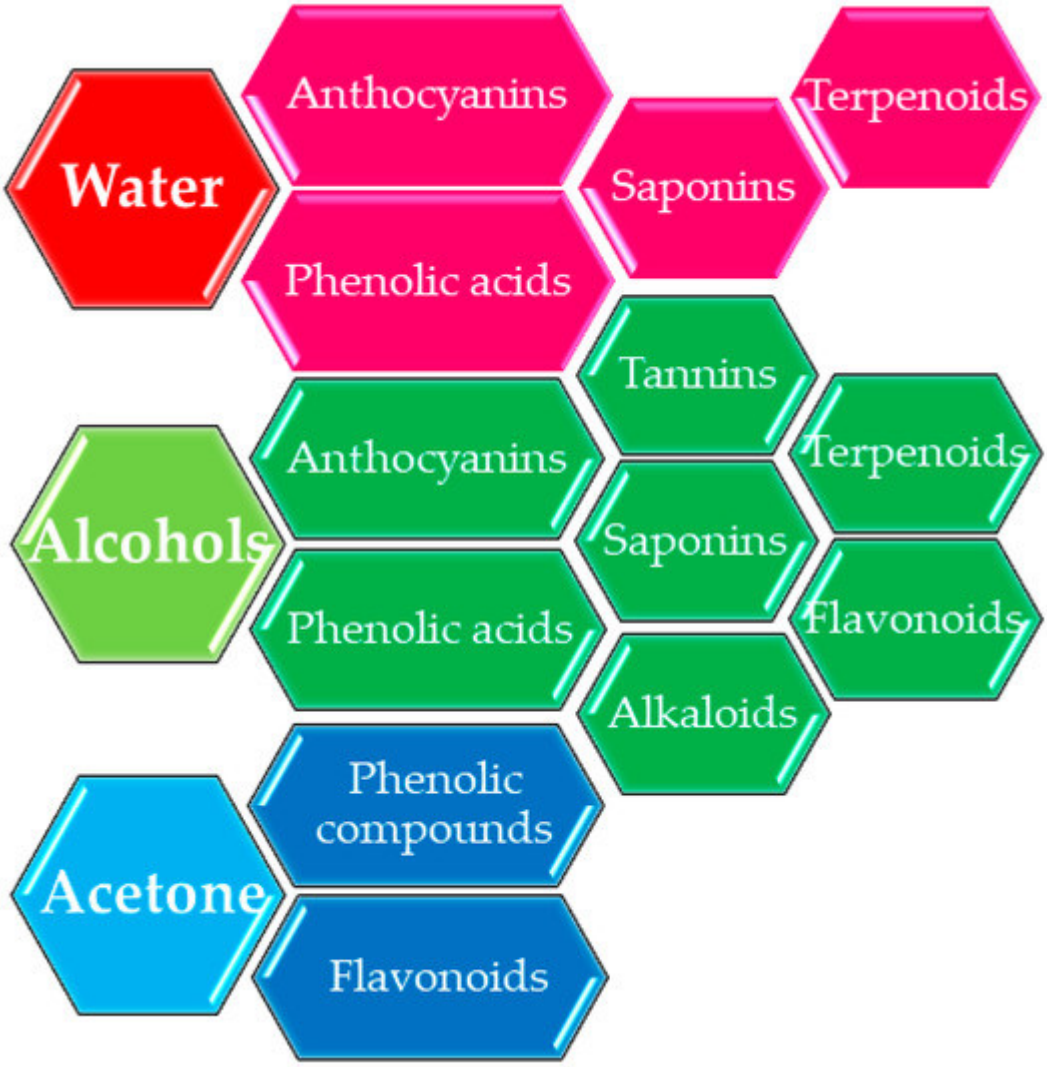

Figure 2. Commonly used solvents in the extraction process.

In the last years, the application of neoteric solvents received special interest, in order to minimize the use of toxic components and maximize the extraction efficiencies, with an emphasis on reducing their toxicity after usage [59]. This category includes ionic liquids and deep (natural) eutectic solvents, which were used due to their possibility toward tailored-extraction, thus increasing extraction efficiency for complex matrixes. Ionic liquids are suitable for different bioactive compounds, such as alkaloids [60] or phenolic compounds [61] due to the good miscibility of target compounds with the solvent. Eutectic solvents have the same properties with ionic liquids, and beside this, they are less toxic and more biodegradable [62]. In addition, bio-based solvents received special interest, such as 2-methyltetrahydrofuran, limonene, or 2-methyltetrahydrofuran, successfully replacing solvents such as n-hexane and toluene with lower production costs and increased biodegradability [63]. Some of these solvents are not commercially available, and they are not still used at an industrial level. Nowadays, the experiment must be carried out with respect to the balance between environment and production costs, in order to achieve full sustainability in the process implementation.

Depending on the plant matrix, temperature is another important parameter that is necessary in the optimization process. Increased temperature can lead to a higher solubility of the analyte, but at the same time, it can lead to the degradation of thermo-sensitive compounds [64]. In the processes where neoteric solvents are used, the temperature significantly modifies the properties of the solvent, thus modifying the solubility of the analytes [65].

The role and optimization of time, pH, solid–liquid ratio, or pressure are discussed in different papers [66][67][68][69][70], as these are significant parameters that can influence the extraction efficiency. Moreover, it cannot be stated than one parameter is more important than another, each of them having a tremendous influence on the overall extraction process results.

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