ACTA
STOMATOLOGICA
CROATICA
www.ascro.hr

Acta Stomatol Croat. 2012;46(4):297-306.
STRUČNI RAD
PROFESSIONAL PAPER

Vice Budimir[1], Vlaho Brailo[2], Ivan Alajbeg[2], Vanja Vučićević Boras[2], Jozo Budimir[3]

Klinička svojstva oralnih lezija uzrokovanih topikalnom primjenom propolisa

Clinical Characteristics of Topical Propolis Induced Oral Lesions

[1] Zavod za ortodonciju Stomatološkog fakulteta Sevučilišta u Zagrebu, Hrvatska
Department of Orthodontics, School of Dental Medicine, University of Zagreb, Croatia
[2] Zavod za oralnu medicinu Stomatološkog fakuleta Sveučilišta u Zagrebu, Hrvatska
Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Croatia
[3] Zavod za oralnu kirurgiju Stomatološkog fakulteta Sveučilišta u Zagrebu, Hrvatska
Department of Oral Surgery, School of Dental Medicine, University of Zagreb, Croatia

Sažetak

Uvod: Propolis, smolasta tvar koju proizvode pčele, uporablja se u narodnoj medicini više od dvije tisuće godina. No, njegovi mnogobrojni sastojci mogu djelovati kao potencijalni antigen. Topikalna primjena može uzrokovati nuspojave u usnoj šupljini. **Materijali i metode:** Retrospektivnom studijom bili su obuhvaćeni pacijenti s oralnim lezijama zbog topikalne uporabe propolisa. Pritom su korišteni podaci iz medicinske dokumentacije pacijenata: izgled i lokalizacija lezija, kada su se pojavili simptomi, terapija i vrijeme cijeljenja te osnovni demografski podaci (dob, spol). **Rezultati:** Sudjelovalo je dvadeset dvoje pacijenata s lezijama uzrokovanima korištenjem propolisa. Najčešća klinička slika bila je erozivni stomatitis. Simptomi su se obično pojavljivali dva i pol dana nakon uporabe propolisa, iako su se neke lezije pojavile odmah. Većina pacijenata (21/22) uspješno je liječena topikalnim kortikosteroidima. Šestero je bilo podvrgnuto alergološkom testiranju – troje je bile pozitivno, a troje negativno. **Zaključak:** Topikalni preparati propolisa mogu prouzročiti teške oralne nuspojave. Dosadašnje spoznaje ne podupiru njegovu široku primjenu u terapiji bolesti usta.

Zaprimljen: 4. lipnja 2012.
Prihvaćen: 20. rujna 2012.

Adresa za dopisivanje
Vlaho Brailo
Sveučilište u Zagrebu
Stomatološki fakultet
Zavod za oralnu medicinu
Gunduliceva 5
10 000 Zagreb, Croatia
brailo@sfzg.hr
faks: +385 1 4830 819
tel: + 385 1 4802 124

Ključne riječi
kožna fistula; zubna pulpa, nekroza; korijenski kanal, preparacija

Uvod

Propolis je smolasta tvar kojom se pčele koriste za gradnju i dezinfekciju košnice (1). Njegov kemijski sastav vrlo je kompleksan. Najčešće se sastoji od 30 posto voska, 55 posto biljnih smola i balzama, 10 posto esencijalnih ulja i 5 posto peludi te biološki aktivnih supstancija poput flavonoida, terpena, pinocembrina, galangina, ferulinske i kofeinske kiseline, estera kofeinske kiseline te cimetne kiseline i cimetnog alkohola (2, 3). Najviše je flavonoida (15 – 27%), biljnih pigmenata čija je uloga u biljkama malo poznata. Koncentracija i udjel navedenih komponenti ovisi o ekološkim i klimatskim čimbenicima koji utječu na biljni izvor korišten pri skupljanju propolisa i zato ih je nemoguće kontrolirati (4).

Uporaba propolisa počela je još prije dvije tisuće godina (4). I tada, kao i danas, ima široku primjenu u medicini, narodnoj medicini i biokozmetici, ponajprije zahvaljujući mnogobrojnim djelovanjima, kao što su antiseptičko, anestetičko, adstrigentno, protuupalno, antibiotsko, antioksidirajuće, protugljivično, protuvirusno i protutumorsko (1, 5, 6). No većina tih svojstava dokazana je u uvjetima *in vitro* ili na laboratorijskim životinjama, dok su kliničke studije na ljudima vrlo rijetke, posebice u slučaju oralnih bolesti (7 – 15).

Introduction

Propolis is a resinous substance used by bees for the construction and disinfection of their hives (1). Chemical composition of propolis is very complex. It normally consists of 30% wax, 55% resins and balsams, 10% essential oils and 5% pollen in addition to biologically active constituents such as flavonoids, terpenes, pinocembrin, galangin, ferulic acid, caffeic acid, caffeic acid esters, cinnamic acid and cinnamyl alcohol (2, 3). Most represented are flavonoids (15-27%), herbal pigments whose role in plants is still not fully understood. Concentration and ratio of various components depend on ecological and climate factors that affect herbal source used for bees' pasture and cannot be controlled (4).

The use of propolis dates back to more than 2000 years (4). Propolis has been and still is widely used in medicine, popular medicine and biocosmetics. Numerous properties have contributed to its widespread use: antiseptic, anesthetic, astringent, anti-inflammatory, antibiotic, antioxidant, antifungal, antiviral and antineoplastic (1, 5, 6). However, the majority of these properties are observed *in vitro* and in laboratory animals, while clinical studies in humans are sparse, especially for oral diseases (7-15).

Važno je istaknuti da je propolis poznat i prema alergijskom potencijalu. Njegovi najjači alergeni su esteri kafeične/kofeinske kiseline (feniletilkafeat i metilbutenilkafeat), iako i ostali sastojci (primjerice, izoferulati, slobodne aromatične kiseline i flavonoidi), ovisno o svojem udjelu, mogu uzrokovati alergijske reakcije (16 – 18). Učestalost alergijskih reakcija na propolis u populaciji iznosi od 1,2 do 6,55 posto (18, 19). Giusti i suradnici (5) zabilježili su kod djece, u razdoblju od 1995. (2%) do 2002. godine (13,7%), izraziti porast godišnje incidencije osjetljivosti na propolis. Isti autori svoje rezultate tumače sve češćom uporabom propolisa u biofarmaceutskim i biokozmetičkim preparatima.

Propolis može djelovati kao kontaktni ili zrakom prenošeni alergen (20). Kontaktni dermatitis najčešći je oblik alergijske reakcije i obično nastaje kod ljudi koji se bave pčelarstvom. Dosad je u literaturi opisano više od 250 slučajeva (20, 21). Zbog sve češćeg korištenja propolisa u medicinskim i kozmetičkim preparatima pčelari danas predstavljaju manje od 25 posto pacijenata alergičnih na propolis (20). Zubne paste, žvakaće gume, oralni antiseptici te mnogi drugi proizvodi za oralnu higijenu koji sadržavaju propolis mogu prouzročiti intra- i perioralne lezije (18, 19, 22 – 27). Ne zna se točno koliko je oralnih alergijskih reakcija uzrokovao propolis. U literaturi je opisano samo šest slučajeva kontaktne alergije (tip IV. – odgođena hipersenzibilnost) na propolis usnoj šupljini (22 – 27). Komercijalni preparati propolisa često sadržavaju mnogo alkohola, što također može uzrokovati lezije oralne sluznice.

Pri uporabi preparata propolisa mogu nastati za život opasne komplikacije, kao što su laringealni edem, anafilaktički šok i akutno zatajenje bubrega (16, 28).

Svrha ovog istraživanja bila je dobiti podatke o osnovnim kliničkim karakteristikama oralnih lezija uzrokovanih topikalnom primjenom propolisa. Istraživanjem su bila obuhvaćena 22 ispitanika.

Ispitanici i postupci

Istraživanjem je bilo obuhvaćeno dvadeset i dvoje pacijenata liječenih u Zavodu za oralnu medicinu Stomatološkog fakulteta u Zagrebu zbog nuspojava nakon topikalne primjene propolisa u usnoj šupljini.

Dijagnoza je postavljena na temelju kliničke slike i anamnestičkih podataka. Korištena je i Naranjova ljestvica za procjenu vjerojatnosti reakcije na lijek (tablica 1.) (29) s pitanjima (koja se različito boduju) o okolnostima nastanka reakcije u odnosu na korištenje određenog lijeka. Konačni zbroj daje podatak o mogućnosti da je reakciju prouzročio određeni lijek.

U istraživanju su se autori služili podacima iz medicinske dokumentacije pacijenata: o izgledu i lokalizaciji lezija, početku pojave simptoma, terapiji i vremenu cijeljenja, te osnovnim demografskim podacima (dob, spol). Zabilježeno je i zašto su se pacijenti koristili propolisom. Sve to uneseno je u radne listove MS Excela i prezentirano deskriptivno.

Godinu dana nakon liječenja pacijenti su bili telefonski intervjuirani. Šesnaestero od njih dvadeset dvoje bilo je dostupno za razgovor. Tada su zamoljeni da se podvrgnu epi-

On the other hand, propolis is well known for its allergenic potential. The most powerful antigenic substances of propolis are esters of the caffeic acid (phenylethyl caffeate and methylbutenyl caffeate), although other ingredients (e.g. isoferulates, free aromatic acids and flavonoids), can cause allergic reactions depending on their share (16-18). The prevalence of allergic reactions to propolis in the population ranges from 1.2% to 6.55% (18, 19). Giusti et al. (5) observed strong increase in propolis sensitivity among children from 1995 (2%) to 2002 (13.7%). The authors believe that the increase in incidence of propolis allergy is a result of its widespread use in biopharmaceutical and biocosmetic products.

Propolis can act as a contact or airborne allergen (20). The most common form of allergic reaction to propolis is contact dermatitis and it usually occurs in beekeepers. More than 250 cases have been described in the literature (20, 21). However, due to its increasing use in medicinal and cosmetic preparations, beekeepers now constitute less than 25% of patients sensitized to propolis (20). Toothpastes, chewing gums, mouthwashes, and various oral hygiene products containing propolis can cause lesions in the oral cavity and perioral tissues (18, 19, 22-27). The exact prevalence of propolis induced oral allergic reactions is not known. So far, six cases of contact allergy (type IV; delayed hypersensitivity) have been reported in the literature (22-27). Commercially available propolis products often contain high content of alcohol which can also be a causative factor for oral mucosal lesions.

Propolis can also cause life threatening reactions such as laryngeal edema, anaphylactic shock and acute renal failure (16, 28).

The aim of the study was to describe clinical characteristics of oral lesions caused by topical application of propolis. We present a series of 22 patients.

Material and methods

A retrospective review of twenty two patients treated at the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, due to side effects of topical propolis use in the oral cavity was made.

The diagnosis was made based on clinical presentation and medical history. Furthermore, Naranjo ADR Probability Scale (Table 1) was used (29). The use of the scale involves answering a series of questions about the adverse event, and then calculating a final score that provides indication of the overall probability that the adverse event represents an adverse reaction to a drug.

Basic demographic data (age, gender) as well as clinical data – appearance and localization of lesions, symptoms onset, treatment and healing time were recorded. Furthermore, reasons for the use of propolis were also recorded. Data were organized in MS Excel worksheets and presented in a descriptive manner.

Telephone interview was conducted 1 year after the treatment. Sixteen out of twenty two patients were available for the interview. During the interview, the patients were invit-

Tablica 1. Naranjova ljestvica
Table 1 Naranjo ADR Probability Scale

1.	Postoje li prethodni izvještaji o nuspojavi na taj lijek? • Are there previous conclusive reports on this reaction? da (+1) Ne (0) ne znam (0) • Yes (+1) No (0) Don't know (0)
2.	Je li nuspojava nastupila nakon primjene suspektnog lijeka? • Did the adverse event appear after the suspected drug was administered? da (+2) ne (0) ne znam (0) • Yes (+2) No (-1) Don't know (0)
3.	Je li se popravila nakon što je prestala uporaba suspektnog lijeka ili nakon što je primijenjen specifični antagonist? • Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered? da (+1) ne (0) ne znam (0) • Yes (+1) No (0) Don't know (0)
4.	Je li se nuspojava ponovno pojavila nakon što je lijek opet primijenjen? • Did the adverse reaction reappear when the drug was readministered? da (+2) ne (-1) ne znam (0) • Yes (+2) No (-1) Don't know (0)
5.	Postoje li alternativni uzročnici (osim lijeka) koji bi mogli samostalno uzrokovati reakciju? • Are there alternative causes (other than the drug) that could on their own have caused the reaction? da (-1) ne (+2) ne znam (0) • Yes (-1) No (+2) Don't know (0)
6.	Je li nuspojava nastupila nakon što je primijenjen placebo? • Did the reaction reappear when a placebo was given? da (-1) ne (+1) ne znam (0) • Yes (-1) No (+1) Don't know (0)
7.	Je li lijek otkriven u serumu (ili drugim tjelesnim tekućinama) u koncentracijama za koje se zna da su toksične? • 7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? da (+1) ne (0) ne znam (0) • Yes (+1) No (0) Don't know (0)
8.	Je li reakcija bila izraženija kod više doze ili manje izražena kod niže doze? • Was the reaction more severe when the dose was increased, or less severe when dose was decreased? da (+1) ne (0) ne znam (0) • Yes (+1) No (0) Don't know (0)
9.	Je li pacijent imao sličnu reakciju na isti ili sličan lijek u nekom od prijašnjih izlaganja? • Did the patient have a similar reaction to the same or similar drug in any previous exposure? da (+1) ne (0) ne znam (0) • Yes (+1) No (0) Don't know (0)
10.	Je li nuspjava potvrđena nekim objektivnim testom? • Was the adverse event confirmed by any objective evidence? da (+1) ne (0) ne znam (0) • Yes (+1) No (0) Don't know (0)

Konačni zbroj daje osnovu za objektivnu procjenu vjerojatnosti nuspojave na lijek • The final score allows some basis for an objective assessment of the likelihood that an ADR may have occurred:
> 9 = jako vjerojatno • highly probable
> 5 - 8 = vjerojatno • probable
> 1 - 4 = moguće • possible
≤ 0 = dvojbeno • doubtful

kutanom alergološkom testiranju na propolis. Četvero su pristali, a kod dvoje pacijenata je alergološko testiranje bilo obavljeno odmah nakon terapije. Prema uputama Helsinške deklaracije, prije postupka su potpisali informirani pristanak. Testiranje je obavljeno izvornom otopinom propolisa, te njezinim 50-postotnim razrjeđenjem. Alkohol i fiziološka otopina korišteni su kao negativne kontrole. Test je nakon 48 sati očitao terapeut koji nije sudjelovao u testiranju, a prema kriterijima Međunarodnog udruženja za istraživanje kontaktnog dermatitisa (30).

Rezultati

Rezultati su predstavljeni u tablici 2. Kod svih pacijenata konačni je rezultat prema Naranjovoj ljestvici bio 6 do 7, što upućuje na to da se radi o mogućoj nuspojavi nakon uporabe propolisa. U istraživanju je sudjelovalo četrnaest žena (u dobi od 18 do 69 godina, prosječna dob 46 godina) i osmorica muškaraca (u dobi od 35 do 80 godina, prosječna dob 42,5 godine).

Šestero od ukupno dvadeset i dvoje (27,27%) pacijenata imali su simptome odmah nakon uporabe propolisa, a kod desetero (45,45%) opaženi su tri do četiri dana poslije početka primjene preparata propolisa. Jedan od dvadeset i dvoje pacijenata (4,55%) naveo je da su se simptomi pojavili za jedan dan, a kod jednoga pacijenta zabilježeni su 15 dana nakon primjene propolisa (4,55%). Četvero od dvadeset i dvo-

ed to undergo patch testing to propolis. Four patients agreed while in two patients the patch test was performed immediately after the treatment. Before the patch test, informed consent according to Helsinki declaration was obtained from each patient. Original propolis solution and 50% dilution were used. Alcohol and saline were used as controls. The test was analyzed after 48 hours by a blinded researcher according to International Contact Dermatitis Research Group criteria (30).

Results

The results are shown in Table 2. In all the patients, the final score of Naranjo ADR Probability Scale was 6-7, indicating that the adverse reaction was caused by propolis. Fourteen of our patients were women (aged 18-69 years, median age 46 years) and 8 were men (aged 35-80 years, median age 42.5 years).

In 6 out of 22 (27.27%) patients, the symptoms occurred immediately after the use of propolis, while in 10 out of 22 (45.45%) patients, the symptoms appeared 2-4 days after the application of propolis. One out of 22 patients indicated that the occurrence of symptoms was within 1 day and, in another patient, 15 days after the application of propolis (4.55% each). Four out of 22 (18.18%) patients could not remember the exact time of onset.

je (18,18%) pacijenata nije se moglo sjetiti koliko vremena je prošlo od početka korištenja preparata propolisa do pojavljivanja simptoma.

U kliničkoj slici većine pacijenata (19 od 22; 86,36%) dominirale su erozije, a kod troje (13,64%) eritem. Kad je riječ o lokalizaciji, promjene su kod sedmero od dvadeset i dvoje (31,82%) pacijenata bile u cijeloj usnoj šupljini, kod petero (22,73%) na usnama, kod dvoje (9,09%) na mekom nepcu, kod dvoje (9,09%) na desnima, kod dvoje (9,09%) na tvrdom nepcu, kod dvoje (9,09%) na jeziku, kod jednoga (4,55%) u vestibulumu te kod još jednoga (4,55%) u dnu usne šupljine. Klinički izgled lezija prikazan je na slici 1.

U terapiji dvadeset i jednog pacijenta (95,45%) korišteni su topikalni kortikosteroidi (betametazonpropionat mast, 0,5% – tri puta dnevno za lokalizirane lezije ili otopina deksametazona 1mg/ml – tri puta dnevno za generalizirane lezije), dok su lezije jedne pacijentice bile tako opsežne da su zahtijevale terapiju sistemskim kortikosteroidima (Prednizon 20 mg/5 dana). Vrijeme cijeljenja kod trinaestero od dvadeset i dvoje (59,09%) pacijenata iznosilo je 6 do 20 dana (prosječno 8 dana), a njih devetero (40,91%) nije došlo na kontrolni pregled nakon sedam dana, pa se pretpostavlja da su lezije uredno zacijelile.

Petero pacijenata (22,73%) koristilo se propolisom za liječenje gingivitisa. Primijenjen je bio i za terapiju iritacije uzrokovane neadekvatnim protetskim nadomjestkom (3 pacijenta; 13,64%), za terapiju afti (također 3 pacijenta; 13,64%), te za terapiju edema donje usne (1 pacijent; 4,55%). Jedan pacijent (4,55%) koristio se propolisom za bržu regeneraciju desni nakon brušenja zuba, a dvoje (9,09%) kao sredstvom za oralnu higijenu. Sedmero pacijenata (31,82%) koristilo se propolisom za *zdravlje usne šupljine*.

Topikalni preparati propolisa koje su primjenjivali pacijenti bili su kapi ili sprej, a jedan je dodatno rabio kremu i bombone s propolisom. U petnaest slučajeva pacijenti su se samoinicijativno počeli koristiti preparatima propolisa, u pet slučajeva to su im savjetovali liječnici opće medicine ili farmaceuti, a dvoje je nabavilo propolis nakon preporuke prijatelja.

Alergološki test bio je pozitivan u tri slučaja, a u druga tri negativan.

Nitko od ispitanih pacijenata nije se ponovno koristio preparatima propolisa niti je ponovno imao slične reakcije u ustima.

Rasprava

U ovoj studiji sudjelovalo je dvadeset i dvoje ispitanika s oralnim nuspojavama nakon korištenja propolisa. Uvjereni smo da su oralne lezije kod naših pacijenata manifestacija alergijske reakcije na propolis. Iako se samo šestero njih podvrgnulo alergološkom testiranju, tipična klinička slika, anamnestički podaci i visok rezultat na Naranjovoj ljestvici upućuju na to da se radi o oralnoj alergijskoj reakciji. U prilog toj tvrdnji jest i činjenica da je antigeni potencijal propolisa jako dobro poznat i dokumentiran, te da su sve opisane nuspojave nakon korištenja propolisa, osim akutnog zatajenja bubrega, alergijske etiologije (16, 18-20, 23 – 26). Alergološko testi-

In majority of patients (19 out of 22; 86.36%), dominant clinical lesions were erosions, while in 3 out of 22 (13.64%) patients, the dominant lesion was erythema. The lesions were scattered throughout the oral cavity in 7 out of 22 (31.82%) patients and in 5 out of 22 (22.73%) patients, they were localized on the lips. In 2 patients (9.09%), the lesions were localized on the meko nepce • soft palate, in 2 patients (9.09%), the lesions were localized on the gingiva, in 2 patients (9.09%), the lesions were localized on the hard palate and in 2 patients (9.09%), the lesions were localized on the tongue, respectively. In one (4.55%) patient, the vestibular mucosa and sublingual mucosa were affected, respectively. Clinical appearance of lesions is presented in Figure 1.

Twenty one patients (95.45%) were treated with topical corticosteroids (betamethasone propionate 0.5% ointment tid for localized lesions or dexamethasone mouthwash 1 mg/ml tid for generalized lesions) while in one patient, the lesions were very extensive and required a use of systemic corticosteroids (Prednisone 20 mg/5 days). The time for lesions to heal was 6-20 days (median 8 days) in 13 out of 22 (59.09%) patients. Nine out of 22 (40.91%) patients did not come to the scheduled follow-up after 7 days, so it can be assumed that the lesions healed properly.

Five patients (22.73%) used propolis for the treatment of gingival inflammation. Propolis was also used for the treatment of denture irritations (3 patients; 13.64%), aphthous ulcerations (3 patients; 13.64%), and lip edema (1 patient; 4.55%). One patient (4.55%) used propolis for the recovery of gingiva after crown preparation and 2 patients (9.09%) used it for oral hygiene. Seven patients (31.82%) used propolis "to maintain good oral health".

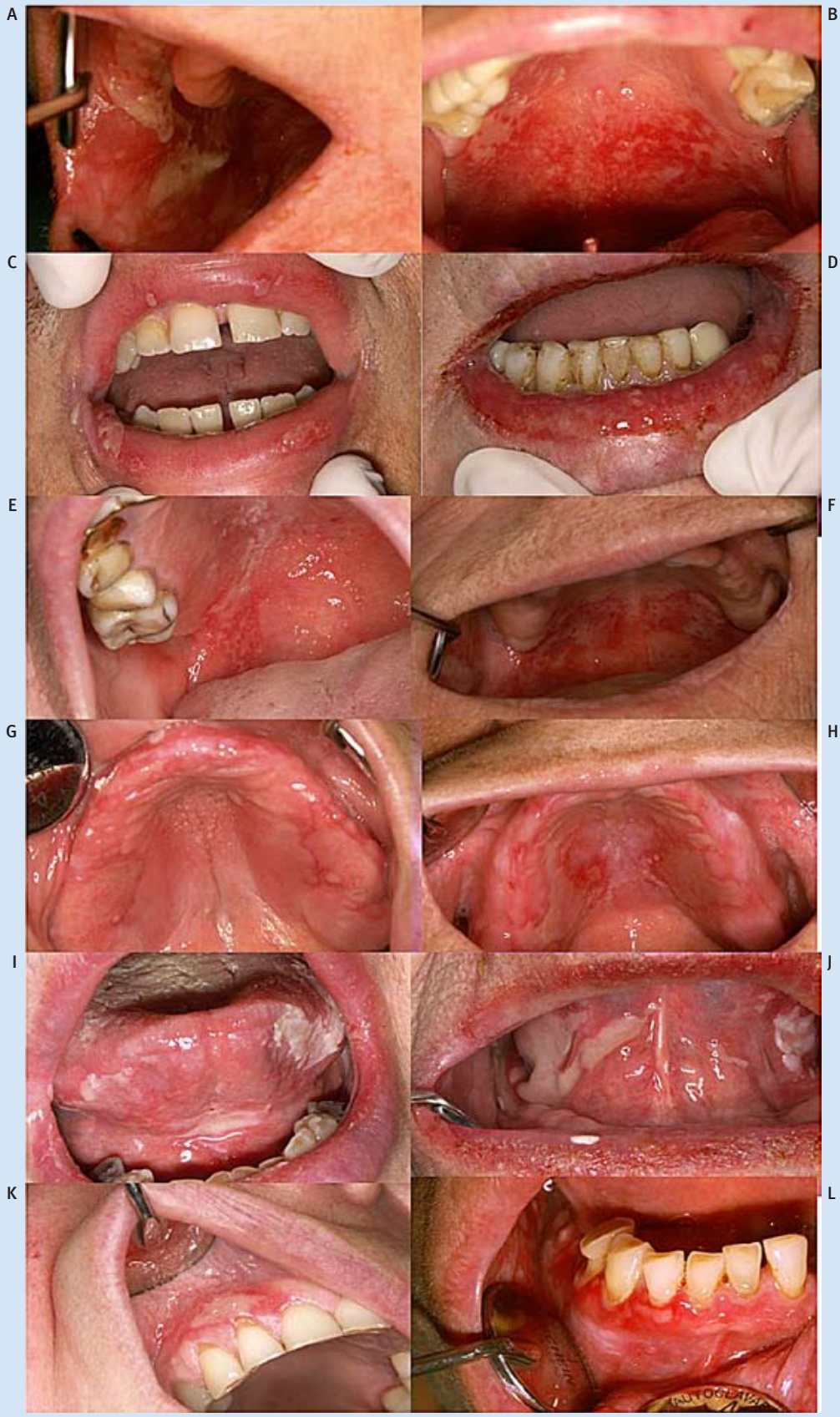
All patients used propolis spray or solution while one patient used propolis enriched creams and candies as well. Propolis was self-prescribed in 15 cases, recommended by a health professional in 5 cases and recommended by a friend in 2 cases.

Patch test was positive in 3 patients and negative in 3 patients as well.

None of the interviewed patients used propolis again and did not experience similar reactions in their mouth.

Discussion

Twenty two patients with oral lesions due to topical application of propolis are presented in this study. We believe that oral lesions in our patients might be a manifestation of propolis allergy. Even though only 6 patients underwent patch testing, typical clinical presentation, patients' history and high scores on Naranjo ADR scale point to the diagnosis of oral allergic reaction. This statement is further corroborated by the fact that the antigenic potential of propolis is well documented and that all side effects of propolis in the literature, except acute renal failure have allergic etiology (16, 18-20, 23-26). In our cohort, patch-testing procedure took



Slika 1. Klinička slika oralnih lezija uzrokovanih topikalnom upotrebom propolisa. Kod većine pacijenata radilo se o erozijma prekrivenim pseudo membranama lokaliziranima u cijeloj usnoj šupljini (A), na mekom nepcu (B,E,F), usnama (C,D), tvrdom nepcu (G,H), dnu usne šupljine (I,J) i gingivi (K,L)

Figure 1 Cinical presentation of topical propolis induced oral lesions. Lesions presented as erosions covered with pseudomembrane that were located on whole oral cavity (A), or were localised on meko nepce • soft palate (B,E,F), lips (C,D), hard palate (G,H), sublingual mucosa (I,J) and on gingiva (K,L).

Tablica 2. Kliničke i demografske karakteristike pacijenata
Table 2 Clinical and demographic characteristics of the patients

Dob • Age	Spol • Sex	Dani do pojave simptoma • Day after symptoms onset	Lokalizacija • Localization	Opis lezija • Type of lesions	Oblik proizvoda • Propolis product
69	ž • f	N/A	cijela usna šupljina • whole mouth	erozije • erosions	sprej • spray
35	m	3	meko nepce • soft palate	erozije • erosions	sprej • spray
37	m	4	usne • lips	erozije • erosions	sprej • spray
43	m	3	cijela usna šupljina • whole mouth	erozije • erosions	kapi • drops
80	m	odmah • immediately	usne • lips	erozije • erosions	kapi • drops
62	ž • f	2	cijela usna šupljina • whole mouth	erozije • erosions	sprej • spray
70	m	N/A	cijela usna šupljina • whole mouth	erozije • erosions	kapi • drops
57	ž • f	4	tvrdo nepce • hard palate	erozije • erosions	sprej • spray
46	m	3	gingiva	eritem • erythema	sprej • spray
46	ž • f	odmah • immediately	dno usne šupljine • sublingual mucosa	erozije • erosions	sprej • spray
34	ž • f	4	gingiva	erozije • erosions	kapi • drops
59	ž • f	3	cijela usna šupljina • whole mouth	erozije • erosions	sprej, kapi, krema, bomboni • spray, drops, creams, candies
49	ž • f	15	tvrdo nepce • hard palate	erozije • erosions	kapi • drops
42	m	odmah • immediately	jezik • tongue	erozije • erosions	sprej • spray
41	m	2	usne • lips	erozije • erosions	sprej • spray
21	ž • f	N/A	usne • lips	eritem • erythema	kapi • drops
52	ž • f	odmah • immediately	vestibulum • vestibular mucosa	erozije • erosions	sprej • spray
28	ž • f	odmah • immediately	jezik • tongue	erozije • erosions	kapi • drops
66	ž • f	3	cijela usna šupljina • whole mouth	erozije • erosions	sprej • spray
46	ž • f	N/A	meko nepce • soft palate	erozije • erosions	sprej • spray
30	ž • f	odmah • immediately	cijela usna šupljina • whole mouth	erozije • erosions	kapi • drops
18	ž • f	1	usne • lips	eritem • erythema	sprej • spray

ranje naših pacijenata obavljeno je mjesec dana do dvije godine nakon liječenja. Oba pacijenta koja smo testirali unutar mjesec dana te jedan koji je testiran nakon dvije godine, bili su pozitivni. Budući da je kod četvero pacijenata prošlo dosta vremena od liječenja do testiranja, nismo mogli nabaviti originalni preparat kojim su se koristili i smatrao se uzročnikom reakcije. Nedostatak studije jest u tome što je za alergološko testiranje četvero pacijenata korišten komercijalni preparat do kojeg smo uspjeli doći. Kao što je već navedeno, udjel različitih kemijskih sastojaka u propolisu ovisi o ispaši pčela i ne može se kontrolirati (4). Pretpostavljamo da u preparatu korištenom za alergološko testiranje nije bilo određenih antigena koji su izazvali reakcije kod pojedinih pacijenata. To je najvjerojatnije objašnjenje zašto je samo troje od šestero pacijenata imalo pozitivan rezultat. Ipak, treba istaknuti da su oba pacijenta koje smo testirali originalnim preparatom kojim su se koristili imali pozitivan alergološki test.

place 1 month to 2 years after the treatment. Both patients that were tested within 1 month along with one patient tested with 2 years delay had a positive patch test. Since in 4 patients the delay from onset to patch testing was substantial, we were unable to obtain and use the specific product which was considered the cause of the reaction. The shortcoming of this study is the fact that for patch testing in 4 patients, instead of using the actual product used at the onset of oral lesions, we had to use one readily available product. As stated previously, ratio of various chemical compounds in propolis depends on herbal source used for bees' pastry and cannot be controlled (4). We assume that the product used for patch testing lacked specific antigens that caused reactions in particular patients. This might explain why only 3 out of 6 patients were tested positive. Nevertheless, we emphasize that both patients tested with the same products they bought and used themselves tested positive.

Terapija • Treatment	Vrijeme cijeljenja • Healing time	Razlog korištenja propolisa • Reason for propolis use	Prema čijoj preporuci • Propolis prescribed by	Naranjov zbroj • Naranjo score
topikalni steroidi • topical steroids	7 dana • days	bez posebnog razloga • no specific reason	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	8 dana • days	bez posebnog razloga • no specific reason	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	6 dana • days	gingivitis • gingival inflammation	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	N/A	gingivitis • gingival inflammation	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	11 dana • days	gingivitis • gingival inflammation	dr. dent. med. • dentist	6
topikalni steroidi • topical steroids	N/A	bez posebnog razloga • no specific reason	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	9 dana • days	bez posebnog razloga • no specific reason	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	20 dana • days	iritacija protezom • denture irritations	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	N/A	bez posebnog razloga • no specific reason	farmaceuta • farmacist	6
topikalni steroidi • topical steroids	8 dana • days	recovery of gingiva after crown preparation	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	N/A	oralna higijena • oral hygiene	prijatelja • friend	6
sistemski steroidi • systemic steroids	15 dana • days	iritacija protezom • denture irritations	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	N/A	gingivitis • gingival inflammation	prijatelja • friend	6
topikalni steroidi • topical steroids	7 dana • days	iritacija protezom • denture irritations	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	7 dana • days	bez posebnog razloga • no specific reason	dr. dent. med. • dentist	7
topikalni steroidi • topical steroids	N/A	afte • aphthous ulcerations	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	N/A	edem usne • lip oedema	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	11 dana • days	afte • aphthous ulcerations	dr. med. • MD	6
topikalni steroidi • topical steroids	N/A	bez posebnog razloga • no specific reason	dr. med. • MD	6
topikalni steroidi • topical steroids	N/A	bez posebnog razloga • no specific reason	samoinicijativno • self-prescribed	6
topikalni steroidi • topical steroids	7 dana • days	afte • aphthous ulcerations	samoinicijativno • self-prescribed	7
topikalni steroidi • topical steroids	10 dana • days	gingivitis • gingival inflammation	samoinicijativno • self-prescribed	7

Ne može se zanemariti, barem kod dijela pacijenata, mogućnost drugog uzroka oralnih lezija, a to je velika količina etanola (50 – 70%) u preparatima propolisa. Etanol se koristi u proizvodnji propolisa te mnogi njegovi preparati dolaze na tržište kao visoko koncentrirane alkoholne otopine (1). Poznato je da etanol može prouzročiti kemijske ozljede sluznice usne šupljine.

Četrnaest (63,64%) pacijenata bilo je ženskog spola, a osam (36.36%) su bili muškarci. Rezultati naše studije slažu se s onima Hausena i suradnika (27) koji su također istaknuli veći udjel žena u populaciji bolesnika alergičnih na propolis. S druge strane Giusti i njegovi kolege (5) zabilježili su više alergija na propolis kod muškaraca. Prema Wöhrlu i suradnicima (18), osjetljivost na propolis najviša je u dječjoj dobi i smanjuje se tijekom života. Najnižu stopu imaju pacijenti stariji od 70 godina.

Kod naših pacijenata lezije su se najčešće pojavljivale u obliku mnogobrojnih erozija po cijeloj usnoj šupljini. U pet

We, however, cannot ignore another possible etiology of oral lesions in, at least, some of the patients: high content of ethanol (50-70%) in propolis products. Ethanol is used for the extraction of propolis during fabrication process and many products are found on market in highly concentrated alcohol solutions (1). Ethanol could possibly cause chemical injury to oral mucosa.

Fourteen patients (63.64%) were female and 8 (36.36%) were male. Our results are in concordance with the results of Hausen et al. (27) who reported a higher frequency of propolis allergy in women. On the other hand, Giusti et al. (5) reported a higher frequency of propolis allergy in men. According to Wöhrl et al. (18), the overall sensitization rate is highest in children and it decreases steadily, to be lowest among patients more than 70 years old.

Most frequent lesions in our patients were multiple erosions throughout the oral cavity. Five out of 22 cases had

slučajeva bile su samo na usnama. Izgled kliničkih promjena i njihove lokalizacije slični su promjenama i lokalizacijama navedenima u literaturi. Fernandez i suradnici (22) opisali su dva slučaja alergijskog kontaktnog stomatitisa. U kliničkoj slici naveli su prisutnost labijalnog edema, edema jezika, bolove te otežan govor i disanje. Hayi i njegovi kolege (24) istaknuli su slučaj oralnog mukozitisa s ulceracijama, a uzrokovale su ga pastile s propolisom. Brailo i suradnici (25) navode opsežne erozije na usnama kao rezultat korištenja propolisa za liječenje recidiva aftoznih ulceracija. Pasolini i kolege (26) izvještavaju o heilitisu zbog višestrukog kontakta usana s medom obogaćenim propolisom. Jensen i Andersen (23) opisali su slučaj 44-godišnje žene kod koje je nastao snažan heilitis praćen intenzivnim eritematoznim dermatitisom lica i vrata nakon što je usne namazala balzamom s propolisom.

Prosječno vrijeme do pojave lezija nakon korištenja propolisa bilo je dva i pol dana (u rasponu od 0 do 15 dana), što se podudara sa slučajevima opisanima u literaturi (8 sati – 10 dana) (22, 25). Münstedt i Kalder (21) navode da su se kožne alergijske reakcije kod pčelara pojavljivale u intervalu od pet minuta do 48 sati nakon izlaganja propolisu.

Zdravstveni djelatnici (liječnici i farmaceuti) savjetovali su uporabu propolisa gotovo petini pacijenata. Vjerujemo da je taj omjer u općoj populaciji još veći jer se neki proizvodi na bazi propolisa nalaze u slobodnoj prodaji kao preparati koji se nabavljaju bez recepta za liječenje različitih bolesti parodonta i oralne sluznice, pa čak i za zubobolju. Iako propolis ima mnogobrojna biološka svojstva, poput antiseptičkog, anestetičkog, protuupalnog, antibiotskog, antioksidacijskog, protugljivičnog, protuvirusnog i protutumorskog, treba istaknuti da se velika većina njih ispitivala u uvjetima *in vitro* i na životinjama (1, 5, 6). Kao što je već navedeno, rijetka su klinička ispitivanja na ljudima, posebice kad je riječ o oralnim bolestima. U trima studijama opisano je protugljivično djelovanje propolisa u liječenju protetskog stomatitisa (7-9). No dvije su (7, 8) bile *open label,* a u jednom eksperimentalnom istraživanju na 30 ispitanika dokazano je da nema znatne razlike između propolisa i mikonazola (9). U eksperimentalnoj studiji provedenoj na 19 ispitanika Sameti i njegovi suradnici (10) istaknuli su da uzimanje 500 miligrama propolisa na dan može smanjiti i broj epizoda rekurentnih aftoznih ulceracija i poboljšati pacijentima kvalitetu života. No, kao što i autori ističu, navedeni rezultati trebali bi se ispitati na većem uzorku u *placebo* kontroliranoj kliničkoj studiji. Murray i suradnici (11) navode da oralni antiseptici koji sadržavaju propolis nemaju značajnijeg utjecaja u inhibiciji formiranja *de novo* plaka u odnosu na kontrole. No u novijim studijama (12 – 15) ističe se određena djelotvornost oralnih antiseptika s propolisom u inhibiciji akumulacije plaka i smanjenju upale desni. I ovi se rezultati također moraju potvrditi u većim i opsežnijim randomiziranim kontroliranim studijama. Sudeći prema podacima iz literature, može se zaključiti da se djelotvornost propolisa u liječenju oralnih bolesti tek treba potvrditi.

Prema našim spoznajama, ovo je prva studija provedena na većoj skupini pacijenata s oralnim lezijama kao nuspojavom nakon korištenja topikalnih preparata propolisa. Na temelju dobivenih rezultata može se zaključiti da od oralnih le-

only their lips affected. Clinical presentation is in concordance with the cases reported in the literature. Fernandez et al. (22) reported two cases of allergic contact stomatitis manifested clinically as labial edema, tongue edema, pain, harsh speech, and mild dyspnoea. Hay et al. (24) reported a case of oral mucositis with ulceration as a result topical use of propolis lozenges. Brailo et al. (25) reported a case of extensive erosions on the lips resulted from the use of propolis for the treatment of recurrent aphthous ulcerations. Pasolini et al. (26) described the appearance of cheilitis induced by repeated contact with propolis enriched honey. Jensen and Andersen (23) reported a case of a 44-year-old woman who experienced serious flare-up of face and neck dermatitis and pronounced cheilitis after using a propolis based lip balm.

Median time for the occurrence of lesions was 2.5 days (range 0-15 days), which is in accordance with oral allergic reactions to propolis reported in the literature (8 hours - 10 days) (22, 25). As described by Münstedt and Kalder (21), the skin allergic reaction to propolis in beekeepers developed after various time intervals ranging between 5 minutes and 48 hours.

It was interesting to note that propolis was recommended by a health professional (dentists, general medicine practitioners and pharmacists) to one fifth of the patients. We believe that this ratio is even higher in general population since some propolis-based products are marketed as OTC remedies for different oral mucosal and periodontal conditions, and even for a toothache. Even though propolis has numerous biological properties such as antiseptic, anesthetic, anti-inflammatory, antibiotic, antioxidant, antifungal, antiviral and antineoplastic, it should be emphasized that a great majority of these properties are reported *in vitro* and in animals (1, 5, 6). As previously stated, clinical trials in humans are sparse, especially for oral diseases. Three studies reported antifungal activity of propolis in the treatment of denture stomatitis (7-9). However, two studies (7, 8) were open label and in one pilot study on 30 participants no significant difference between propolis and miconazole was observed (9). In their pilot study on 19 participants, Samet et al. (10) reported that systemic ingestion of 500 mg of propolis per day may lead to a decrease in aphthous ulcer outbreaks and an improvement in the patient's quality of life. However, as authors indicated, these findings should be evaluated in a larger sample clinical trial. Murray et al. (11) reported that propolis-containing mouthrinse was not significantly efficient in the inhibition of *de novo* plaque formation compared to negative controls. More recent studies (12-15), on the other hand, reported some efficacy of propolis mouthwash in the inhibition of plaque accumulation and reduction of gingival inflammation. Again, these findings need to be confirmed in larger and more robust randomized controlled trials. Judging from the literature data, we may conclude that the efficacy of propolis for the treatment of oral diseases still needs to be determined.

To our knowledge, this is the first report of a larger series of patients who developed oral lesions due to topical application of propolis. Based on the results of this study, it can be concluded that oral lesions caused by topical use of

zija uzrokovanih propolisom češće pate žene i da zahvaćaju sve dobne skupine. U kliničkoj slici dominira erozivna upala koja zahvaća cijelu usnu šupljinu, ali lezije se mogu pojaviti i lokalizirano, najčešće na usnama. Simptomi obično nastaju dva i pol dana nakon uporabe propolisa, ali mogu i odmah. Lezije se uspješno liječe topikalnim kortikosteroidima, no u rijetkim slučajevima potrebna je terapija sistemskim kortikosteroidima. Ovisno o opsežnosti lezija, vrijeme cijeljenja iznosi šest do dvadeset dana.

S obzirom na slučajeve opisane u ovoj studiji, te one iz literature, možemo zaključiti da uporaba propolisa kod pojedinaca može rezultirati ozbiljnim nuspojavama. Smatramo da se propolis ne bi trebao uporabljati za liječenje bolesti usne šupljine jer dosadašnje spoznaje ne podupiru njegovu primjenu.

propolis occur more frequently in women and affect all age groups. Dominant clinical presentation is erosive stomatitis, but lesions can also be localized, most frequently on the lips. Symptoms usually appear 2.5 days after the use of propolis, although they can occur immediately. The lesions are successfully treated with topical corticosteroids, but on rare occasions, it is necessary to introduce systemic corticosteroid therapy. Depending on the extensiveness of the lesions, healing time is 6-20 days.

Bearing in mind cases presented in this series and cases reported in the literature, we can conclude that in some people propolis application can result in serious side-effects. We also believe that topical propolis should not be used for the treatment of oral diseases as current knowledge does not support its widespread use.

Abstract

Objectives: Propolis, a resinous substance produced by bees, has been used in popular medicine for more than 2000 years. **Material and methods:** Numerous compounds of propolis can act as potent sensitizers. Topical application of propolis can induce oral lesions. Patients with oral lesions due to topical propolis are presented. Basic demographic (age, gender) and clinical data (appearance and localization of the lesions, symptoms onset, treatment and healing time) were recorded. **Results:** Twenty two patients with propolis-induced lesions were evaluated. The most common occurring presentation was erosive stomatitis. Symptoms tended to appear 2.5 days after propolis use although some lesions occurred immediately after utilization. Majority of patients (21/22) were successfully treated with topical corticosteroids. Six patients underwent patch testing, 3 patients were positive and 3 were negative. **Conclusion:** Topical propolis can have serious oral side effects. Current knowledge does not support its widespread use in the treatment of oral diseases.

Received: June 4, 2012
Accepted: September 20, 2012

Address for correspondence
Vlaho Brailo, DMD, PhD
Department of Oral Medicine
School of Dental Medicine
University of Zagreb
Gunduliceva 5
10 000 Zagreb, Croatia
Fax: +385 1 4830 819
Tel: + 385 1 4802 124
brailo@sfzg.hr

Key words
Cutaneous Fistula; Dental Pulp Necrosis; Root Canal Preparation

References

1. Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). Food Chem Toxicol. 1998 Apr;36(4):347-63.
2. Scully C. Propolis: a background. Br Dent J. 2006 Apr 8;200(7):359-60.
3. Kosalec I, Bakmaz M, Pepeljnjak S, Vladimir-Knezević S. Quantitative analysis of the flavonoids in raw propolis from northern Croatia. Acta Pharm. 2004 Mar;54(1):65-72.
4. Castaldo S, Capasso F. Propolis, an old remedy used in modern medicine. Fitoterapia. 2002 Nov;73 Suppl 1:S1-6.
5. Giusti F, Miglietta R, Pepe P, Seidenari S. Sensitization to propolis in 1255 children undergoing patch testing. Contact Dermatitis. 2004 Nov-Dec;51(5-6):255-8.
6. Russo A, Longo R, Vanella A. Antioxidant activity of propolis: role of caffeic acid phenethyl ester and galangin. Fitoterapia. 2002 Nov;73 Suppl 1:S21-9.
7. Ota C, Unterkircher C, Fantinato V, Shimizu MT. Antifungal activity of propolis on different species of Candida. Mycoses. 2001 Nov;44(9-10):375-8.
8. Santos VR, Pimenta FJ, Aguiar MC, do Carmo MA, Naves MD, Mesquita RA. Oral candidiasis treatment with Brazilian ethanol propolis extract. Phytother Res. 2005 Jul;19(7):652-4.
9. Santos VR, Gomes RT, de Mesquita RA, de Moura MD, França EC, de Aguiar EG et al. Efficacy of Brazilian propolis gel for the management of denture stomatitis: a pilot study. Phytother Res. 2008 Nov;22(11):1544-7.
10. Samet N, Laurent C, Susarla SM, Samet-Rubinsteen N. The effect of bee propolis on recurrent aphthous stomatitis: a pilot study. Clin Oral Investig. 2007 Jun;11(2):143-7.
11. Murray MC, Worthington HV, Blinkhorn AS. A study to investigate the effect of a propolis-containing mouthrinse on the inhibition of de novo plaque formation. J Clin Periodontol. 1997 Nov;24(11):796-8.
12. Koo H, Cury JA, Rosalen PL, Ambrosano GM, Ikegaki M, Park YK. Effect of a mouthrinse containing selected propolis on 3-day dental plaque accumulation and polysaccharide formation. Caries Res. 2002 Nov-Dec;36(6):445-8.
13. Pereira EM, da Silva JL, Silva FF, De Luca MP, Ferreira EF, Lorentz TC et al. Clinical evidence of the efficacy of a mouthwash containing propolis for the control of plaque and gingivitis: A phase II study. Evid Based Complement Alternat Med. 2011;2011:750249.
14. Dodwad V, Kukreja BJ. Propolis mouthwash: A new beginning. J Indian Soc Periodontol. 2011 Apr;15(2):121-5.
15. Gebaraa EC, Pustiglioni AN, de Lima LA, Mayer MP. Propolis extract as an adjuvant to periodontal treatment. Oral Health Prev Dent. 2003;1(1):29-35.
16. Hsu CY, Chiang WC, Weng TI, Chen WJ, Yuan A. Laryngeal edema and anaphalactic shock after topical propolis use for acute pharyngitis. Am J Emerg Med. 2004 Sep;22(5):432-3.
17. Wöhrl S, Hemmer W, Focke M, Götz M, Jarisch R. Patch testing in children, adults, and the elderly: influence of age and sex on sensitization patterns. Pediatr Dermatol. 2003 Mar-Apr;20(2):119-23.
18. Wöhrl S, Hemmer W, Focke M, Götz M, Jarisch R. The significance of fragrance mix, balsam of Peru, colophony and propolis as screening tools in the detection of fragrance allergy. Br J Dermatol. 2001 Aug;145(2):268-73.
19. Reider N, Komericki P, Hausen BM, Fritsch P, Aberer W. The seamy side of natural medicines: contact sensitization to arnica (Arnica montana L.) and marigold (Calendula officinalis L.). Contact Dermatitis. 2001 Nov;45(5):269-72.
20. Garrido Fernández S, Arroabarren Alemán E, García Figueroa BE, Goienetxe Fagoaga E, Olaguibel Rivera JM, Tabar Purroy AI. Direct and airborne contact dermatitis from propolis in beekeepers. Contact Dermatitis. 2004 May;50(5):320-1.
21. Münstedt K, Kalder M. Contact allergy to propolis in beekeepers. Allergol Immunopathol (Madr). 2009 Nov-Dec;37(6):298-301.

22. Garrido Fernández S, Lasa Luaces E, Echechipía Modaz S, Arroabarren Alemán E, Anda Apiñániz M, Tabar Purroy AI. Allergic contact stomatitis due to therapeutic propolis. Contact Dermatitis. 2004 May;50(5):321.
23. Jensen CD, Andersen KE. Allergic contact dermatitis from cera alba (purified propolis) in a lip balm and candy. Contact Dermatitis. 2006 Nov;55(5):312-3.
24. Hay KD, Greig DE. Propolis allergy: a cause of oral mucositis with ulceration. Oral Surg Oral Med Oral Pathol. 1990 Nov;70(5):584-6.
25. Brailo V, Boras VV, Alajbeg I, Juras V. Delayed contact sensitivity on the lips and oral mucosa due to propolis-case report. Med Oral Patol Oral Cir Bucal. 2006 Jul 1;11(4):E303-4.
26. Pasolini G, Semenza D, Capezzera R, Sala R, Zane C, Rodella R et al. Allergic contact cheilitis induced by repeated contact with propolis-enriched honey. Contact Dermatitis. 2004 May;50(5):322-3.
27. Hausen BM, Evers P, Stüwe HT, König WA, Wollenweber E. Propolis allergy (IV). Studies with further sensitizers from propolis and constituents common to propolis, poplar buds and balsam of Peru. Contact Dermatitis. 1992 Jan;26(1):34-44.
28. Li YJ, Lin JL, Yang CW, Yu CC. Acute renal failure induced by a Brazilian variety of propolis. Am J Kidney Dis. 2005 Dec;46(6):e125-9.
29. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981 Aug;30(2):239-45.
30. Fregert S. Manual of Contact Dermatitis. On behalf of the International Contact Dermatitis Research Groupand the North American Contact Dermatitis Group. Copenhagen: Munksgaard Publishers; 1981.