Am J Otolaryngol 39 (2018) 759–763

Contents lists available at ScienceDirect

Am J Otolaryngol

journal homepage: www.elsevier.com/locate/amjoto

Honey can help in herpes simplex gingivostomatitis in children: Prospective randomized double blind placebo controlled clinical trial

Osama G. Abdel-Naby Awad*, Abdel-Monem H. Hamad

Otolaryngology, Head and Neck Department, Minia University Hospital, Minia, Egypt

A B S T R A C T

Purpose: Herpes simplex gingivostomatitis (HSGS) in children is a common painful infectious disease. This study aims to examine the combined efficacy of honey with acyclovir suspension compared to acyclovir alone for treating HSGS in young children.

Material and methods: This Randomized double blind placebo controlled study was conducted from June 2015 to September 2017 in a tertiary referral hospital. One hundred children aged 2–8 years with HSGS were randomly classified into 2 groups; study group: treated with honey plus oral acyclovir and control group: treated with oral acyclovir alone. Severity of oral lesions, Fever, eating and drinking ability, pain scores and need for analgesics were compared between 2 groups on day 3, 5 and 7 after starting treatment.

Results: Children receiving honey plus acyclovir (i.e. study group) had significantly earlier disappearance of herpetic oral lesions; median 3 days vs. 6 days in control group (P = 0.022), drooling; 2 days vs. 4 days (P = 0.030) and eating difficulty; 3 days vs. 8 days (P = 0.001). Study group also had significantly lower pain scores, better eating and drinking ability and significantly less need for analgesics at 3 time-points of assessment. Fever disappeared in both groups with no statistically significant difference.

Conclusions: The combined use of honey with oral acyclovir can produce favorable outcome than acyclovir alone in children with Primary herpetic gingivostomatitis.

1. Introduction

Primary herpetic gingivostomatitis (PHGS) is the most commonly observed clinical manifestation of primary herpes simplex virus (HSV) infection, occurring in 25–30% of affected children [1]. About, 90% of cases are caused by HSV-1, detection of HSV-2 has also been reported. There are two peaks with respect to the age at which PHGS occurs. The first peak occurs in children aged between 6 months and 5 years, and the second peak occurs in young adults in their early 20s [2]. In rare cases, PHGS can occur in neonates, in adults, and even in the elderly [3,4]. Individuals in developing countries with a lower socio-economic status become sero-positive for HSV-1 at an earlier age than their counterparts in developed countries [5]. Clinical features of PHGS include a prodrome of fever and constitutional symptoms, followed by oral and extra-oral lesions. The lesions begin as vesicles, which coalesce to form painful ulcers with generalized edematous and bleeding gingivae. Associated findings include fever, bad breath, refusal to drink, anorexia, and submandibular or cervical lymphadenitis. Lesions may involve buccal mucosa, tongue, posterior pharynx, and any gingival and palatal mucosa. Moreover, the affected gingivae often exhibit discernible erosions along the mid-facial free gingival margins, and these may precede the appearance of the mucosal vesicles [6,7,8].

Parenteral acyclovir has been shown to be effective in HSV infections such as encephalitis [9], primary genital herpes [10], and herpes neonatorum. Oral acyclovir has been used successfully to treat genital herpes [11], recurrent herpes labialis and for PHGS [12]. Along with acyclovir, other drugs are used for lowering pain such as non-steroidal anti-inflammatory drugs (NSAIDS), topical anesthetizing sprays, or sucralfate [11,13,14], however; the efficacy and side effects of these agents necessitate more surveys to find the suitable pain relieving drugs beside acyclovir.

Honey, a sweet liquid, is prepared by honeybees from natural sugar solutions, called 'nectar' with the addition of enzymes and evaporation of water. It has been shown to possess antibacterial and anti-inflammatory properties [15]. It is a long time that honey is used for its biological and therapeutic effects. Ancient Egyptians used honey for treatment of the corneal and conjunctival inflammation, and burns at about 5000 years ago [16]. In modern medicine, honey has been used successfully in treatment of burns, split-thickness skin graft donor site, necrotizing fasciitis, infected surgical and diabetic wounds, and corneal lesions. It has been reported to decrease post-tonsillectomy pain, inflammation and significantly improve healing of the tonsillar fossa. It has been found out that thanks to its built-in antioxidant, antibacterial and antiviral and anti-inflammatory impact, honey reduced the toxic impact of chemotherapy and radiotherapy on oral mucosa namely the formation of mucositis and that lessened its intensity and increased the

* Corresponding author at: Otolaryngology, Head and Neck Department, Minia University Hospital, 122 Kornish El-Neel Street, Minia City 61111, Minia, Egypt.
E-mail address: Usama.abdelnabi@mu.edu.eg (O.G. Abdel-Naby Awad).

https://doi.org/10.1016/j.amjoto.2018.09.007
Received 29 June 2018

healing [17–19].

Pain is the most common clinical problem of PHGS and it can affect food intake, hydration, sleep, physical well-being, as well as psychological status of the patients and family. An improvement in pain may improve these and related outcomes, such as recovery, return to schools and use of painkillers [12]. This randomized, double blind, controlled study was designed to examine the effect of honey administration on pain and healing of PHGS lesions along with acyclovir suspension in children.

2. Methods

This prospective randomized study was conducted during the period from June 2015 to September 2017 and was approved by the Committee for Medical Research Ethics in Egypt, 2015NBA5732814. All patients' parents signed a written consent prior to inclusion in the study.

2.1. Patient population

One hundred children aged 2–8 years of age with laboratory evidence of herpes simplex virus infection (positive culture results) and clinical manifestation of PHGS were presented to otolaryngology, Head and Neck surgery department, Minia University Hospital, Minia, Egypt. No pharmaceutical companies funded the study or contributed to the study design, outcome evaluation or writing of this study.

After a swab from the oral lesions for viral cultures and blood for serological tests for HSV were obtained. Patients with positive culture results for HSV, positive serology results for HSV and with clinical picture of PHGS were enrolled in the study. The patients were randomized alternatively divided into 2 groups: control group: treated with acyclovir suspension plus placebo and study group: treated with acyclovir suspension plus honey. Control group was treated with acyclovir in a dose of 15 mg/kg (0.375 ml/kg), five times a day (up to a maximum of 200 mg per dose) for a period of seven days [12] plus placebo in a dose of a tea spoon (5 ml) of sugar syrup in honey-like concentration, consistency and coloring (no artificial color or flavor was added) every 4 h and the patient was asked to swallow slowly over few minutes. Study group was treated with acyclovir in the same dose of control group plus honey dose as a tea spoon (5 ml) of locally or commercially available honey orally every 4 h and the patient was asked to swallow slowly over few minutes. Parents were asked to give acetaminophen to their children in a dose of 15 mg/kg/dose according to patient's request and severity of pain. To prevent bias, the study was designed double blinded, and none of the patients and their parents knew what their group.

We excluded from the study: (1) patients with negative viral cultures and serological tests for HSV even in presence of suspected clinical manifestations, (2) patients with positive serological tests for HSV and negative viral cultures, (3) patients were suspected to be allergic to honey, (4) patient were diagnosed with diabetes mellitus, and (5) patients who disliked taking honey.

2.2. Patients assessment

On enrolment (day 0), a medical history was taken and physical examination was performed. On clinical evaluation: fever, severity of oral lesions, drooling, drinking and eating difficulties were noted. The clinical examination was repeated on days 3, 5, 7 (the day of ending the treatment) for every patient and each of the following parameters was assessed with the assistance of parents' reports:

1. The degree of oral lesions severity

We classified oral lesions severity as Amir et al. [12] described in their study: mild (up to 10 lesions on the tongue or oral mucous membrane), moderate (11 to 20 lesions with swelling of the gums), or severe (> 20 on the tongue or oral lesions and gum lesions).

2. Pain was assessed through:

A. Wong-Baker FACES pain scale: Facial Expressions Grading Scale was developed by Donna Wong and Connie Morain Baker in 1981 and was revised in 1983. There are six facial expressions on the scale. The lowest score is “0” while the highest one is “5”. As the score received from the scale increases, the pain tolerance decreases and as the score decreases the tolerance increases. While applying the scale; the state of having no pain is expressed with a happy face while those who feel a bit pain or quite painful express themselves with a sad face: “This face … “0” So happy cause have no pain, “1”, Got a bit pain, “2” Got a bit more pain, “3” The pain is denser, “4” Got quite a lot pain, “5” Got the highest pain you could imagine. Then the child is told to pick the face that expresses his/her pain the best [20].
B. Visual analogue scale (VAS): was applied for subjective assessment of pain in older children to change subjective data into numerical. There is a 100 mm-long triangle atilt. The top of the triangle is colorless and “0” in measurement. As went down the bottom of the triangle, the color gets darker and the one at the very bottom is, thus, the darkest color. There is a connected indicator among the sides of the triangle. There is a 100 mm of sensitive measurement at the back side of the triangle. Two end definitions of the parameter that will be evaluated on both sides of this measurement are written (No pain…..Excruciating Pain) and the patient is asked to define his/her own status on the triangle with the indicator. The back side of the scale is turned and the pain level of the patient is determined as a result of the 100 mm measurement [20].

3. Eating and drinking ability: was classified as normal, less than normal and unable to eat or drink.
4. The numbers of painkiller doses taken daily to control pain.

The patients were enquired about any systemic side effect or complication on taking acyclovir or honey. The parents recorded the child's symptoms. Compliance was measured by the volume of suspension left in the bottle. A single investigator (O.A.) carried out the follow-up evaluation of all the children.

2.3. Statistical analysis

The Statistical Package of Social Science version 15.0 (SPSS, Chicago, Illinois, USA) was used for data analysis. The quantitative data were presented by mean, median and standard deviation. The times of disappearance of symptoms (mouth lesions, fever, drooling, and eating and drinking difficulties) were compared by the Mann-Whitney non-parametric test. The *t*-test was applied to compare the groups with respect to the continuous variables. Fisher's exact test was used to determine differences in the level of compliance. The probability of < 0.05 was used as a cut-off point for all significant tests.

3. Results

One hundred children were enrolled in the study. Fifty children were randomly allocated to receive acyclovir and placebo (control group) and 50 children to receive acyclovir and honey (study group). Totally, 47 children were boys (47%), and 53 children were girls (53%). There was no significant difference between groups in gender and age. On enrolment both groups had no statistically significant difference regarding demographic variables, duration and severity of clinical symptomatology (Tables 1, 2).

Table 1
Demographic and clinical variables of 2 groups at the start of treatment.

	Study group (50 patients)	Control group (50 patients)
Male: female	23:27	22:28
Age [years]: mean [SD; range]	5.1 (4; 2–8)	6.4 (5; 3–8)
Weight (kg): mean (SD; range)	15.6 (5; 10.7–46.0)	14.2 (4; 11.2–44.0)
No of days' duration (SD) of oral lesions	3.0 (0.3)	4.0 (0.2)
Severity of oral lesions		
Mild	10	11
Moderate	22	24
Severe	18	15
Eating and drinking ability		
Normal	0	0
Less than normal	15	12
Unable to eat	35	38

SD = standard deviation.

Table 2
Median (range) duration (in days) of clinical variables after starting treatment.

Clinical variables	Study group (50 patients)	Control group (50 patients)	P value
Oral lesions	3 (1–7)	6 (3 – 13)	0.022*
Fever	1 (1–4)	2 (1–5)	0.233
Extra-oral lesions	2 (0–7)	3 (0–7)	0.223
Drooling	2 (1–5)	4 (3–8)	0.030*
Eating and drinking difficulties	3 (2–6)	8 (4–12)	0.001*

Mc-Nemer test for comparing clinical variables.
* Significant difference (P-value < 0.05).

3.1. Severity of oral lesions

At the beginning of the study; both groups had no statistically significant difference regarding severity and duration of oral lesions (Tables 1, 2). Patients in study group had statistically significant improvement in severity of their oral lesions compared to control group at 3rd, 5th and 7th days (Table 3). At the end of treatment on day 7; 6 children in study group had oral lesions compared with 14 children in the control group (P = 0.003).

3.2. Fever

The fever disappeared in both groups with no-statistically significant difference (median 1 day vs. 2 days in study group and control group respectively) (Table 2).

3.3. Eating and drinking ability

On enrolment; all the children had eating and drinking difficulties (Table 1). Patients in study group had statistically significant improvement in eating and drinking ability compared to control group at 3rd, 5th and 7th days (Table 4). At the end of treatment on day 7; 5 children in study group had some eating and drinking inability compared with 10 children in the control group (P = 0.030).

3.4. Pain

At the start of the study; both groups had no statistically significant difference regarding their pain scores (Table 5). Patients in study group had statistically significant improvement in severity of pain scores compared to control group at 3rd, 5th and 7th days (Table 5).

3.5. Need for painkiller doses

Patients in study group had statistically significant less number of painkiller doses compared to control group at 3rd, 5th and 7th days (Table 6).

3.6. Compliance

35 children in the control group and 38 in the study group received > 80% of the prescribed treatment, and the rest used 50–80% (P = 0.117).

3.7. Side effects

No significant side effects were recorded in either group. 3 children in study group and 4 patients in control group had mild gastrointestinal symptoms that resolved spontaneously after 24 to 48 h without a change in the study treatment.

4. Discussion

Herpes gingivostomatitis is a contagious disease, especially among children in closed communities or day care centres [21]. Data regarding intra-familial transmission are unclear. In young children HSV is transmitted primarily by contact with infected oral secretions. Treatment with oral acyclovir suspension, started during the first three days of the appearance of herpetic gingivostomatitis and continued for seven days was shown to be significantly more effective than placebo in reducing the severity of the clinical symptoms and shortening the period of infectivity as a result of viral shedding [12].

The most common morbidities after PHGS in children are pain, edema and poor oral intake. Controlling pain is a challenging task in those patients. Pain is due to inflammation, nerve irritation and pharyngeal spasm [22]. Honey significantly improved herpetic pain, eating and drinking ability and consumption of painkillers compared to control in our study. We used Wong-Baker FACES pain scale as it was indicated that children liked this scale the most when compared with the other pain measurement tools and that it also provided the most accurate pain measurement. Also we used VAS in older children as there is no language for the measurement, very easy to apply and VAS has long been known by people, validated and has been accepted in the literature for a long time [20].

The beneficial effect of honey plus acyclovir was evident in most of clinical variables evaluated in our study. We have used commercially or locally available honey for this purpose. In a meta-analysis held by Wijesinghe et al. [23] it was reported that those studies indicated

Table 3
Change of severity of oral lesions in both groups.

Group	Third day					Fifth day					Seventh day				
	No	Mi.	Mo.	Sev.	P-value	No	Mi.	Mo.	Sev.	P-value	No	Mi.	Mo.	Sev.	P-value
Study group (n = 50)	0	2	16	12	< 0.001*	5	27	10	8	< 0.001*	44	6	0	0	0.003*
Control group (n = 50)	0	10	18	13		1	22	15	11		36	11	2	1	

Wilcoxon signed-rank test for comparing change of severity of oral lesions. No = no lesions, Mi. = mild, Mo. = moderate and Sev. = severe.
* Significant difference (P-value < 0.05).

Table 4
Change of eating and drinking ability of 2 groups in the 3rd, 5th and 7th days after starting treatment.

Group	Third day				Fifth day				Seventh day			
	Eating ability			P-value	Eating ability			P-value	Eating Ability			P-value
	N	L	U		N	L	U		N	L	U	
Study group (n = 50)	3	35	12	0.020*	15	33	2	0.010*	45	5	0	0.030*
Control group (n = 50)	0	28	22		7	39	4		40	10	0	

Wilcoxon signed-rank test for comparing change of eating and drinking ability. N = normal, L = less than normal, U = unable to eat.
* Significant difference (P-value < 0.05).

Table 5
Pain scores of 2 groups in the 1st, 3rd, 5th and 7th days after starting treatment (variables are expressed as mean ± SD).

Group	First day		Third day		Fifth day		Seventh day	
	Pain score	P-value	Pain Score	P-value	Pain score	P-value	Pain score	P-value
Study group	7.2 ± 0.21	1.001	5.4 ± 0.56	0.005*	3.23 ± 0.12	0.007*	2.45 ± 0.11	0.001*
Control group	7.1 ± 0.34		6.7 ± 0.43		4.32 ± 0.56		3.87 ± 0.44	

Mc-Nemer test for comparing pain scores.
* Significant difference (P-value < 0.05).

Table 6
Number of painkiller doses taken in the 3rd, 5th and 7th days in both groups after starting treatment (variables are expressed as mean ± SD).

Group	Third day		Fifth day		Seventh day	
	Painkiller	P-value	Painkiller	P-value	Painkiller	P-value
Study group	2.23 ± 0.83	< 0.001*	1.45 ± 0.57	0.040*	0.31 ± 0.35	0.020*
Control group	3.34 ± 1.05		2.71 ± 1.13		1.12 ± 0.79	

Mc-Nemer test for comparing number of painkiller doses.
* Significant difference (P-value < 0.05).

greater efficacy of honey compared with alternative dressing treatments for superficial or partial thickness burns. Macroscopic and microscopic studies under in vivo assessment suggested that the topical application of honey influences the various phases of burn and wound healing [24]. Honey is easily accessible, non expensive and without any specific side effects. The antibacterial property of honey was first recognized by Vanketel in 1895 [25]. The anti-inflammatory activity of honey has been studied in various clinical trials where it decreased severity of mucositis in post radiotherapy cases [26], in treatment of gingivitis [27] and in ophthalmological inflammations [28]. In a study honey has been found to be inhibitory to both gram positive and gram negative bacteria and to both aerobes and anaerobes including *Staphylococcus aureus* and pseudomonas [29]. The data show that the wound healing properties of honey include stimulation of tissue growth, enhanced epithelialization, and minimized scar formation. These effects are ascribed to honey's acidity, hydrogen peroxide content, osmotic effect, nutritional and antioxidant contents, stimulation of immunity, and to unidentified compounds. Prostaglandins and nitric oxide play a major role in inflammation, microbial killing, and the healing process. Honey was found to lower prostaglandin levels prostaglandins (PG) E2 [30], PG 2a [31], thromboxane B2 [32] and elevate nitric oxide end products. These properties might help to explain some biological and therapeutic properties of honey, particularly as an antibacterial agent or wound healing.

The clinical manifestation of herpetic gingivostomatitis varies from a mild illness to a severe course with admission to hospital. In the control group; oral lesions, eating and drinking difficulties were found in a significant number of children for seven days compared to study group. During this period, the sick children were unable to attend day care or kindergarten. Although this study did not attempt to address the economic issue of treatment in PHGS, the significant reduction in the duration of illness is likely to allow children and parents to return to their normal life earlier.

Our study is the first study (up to our knowledge) to address the beneficial effect of honey in children with PHGS, However; there were some limitations in this study such as relatively small number of patients and misunderstanding of the details of VAS by some patients. We conducted this study in university hospital and no companies had any role in the design and conduct of the study, collection, management, and analysis of the data; or preparation, review, and approval of the manuscript.

5. Conclusion

The combined use of acyclovir with honey have produced favorable outcome than acyclovir alone in patients with Primary herpetic gingivostomatitis. Addition of honey can cause improvement of inflammation and may decrease pain, resumption of normal diet and recovery in these patients.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Amir J, Harel L, Smetana Z, Varsano I. The natural history of primary herpes simplex type 1 gingivostomatitis in children. Pediatr Dermatol 1999;16:259–63.
[2] Ajar AH, Chauvin PJ. Acute herpetic gingivostomatitis in adults: a review of 13 cases, including diagnosis and management. J Can Dent Assoc 2002;68:247–51.
[3] Whitley RJ. Herpes simplex virus infections. In: Glaser R, Jones JF, editors. Herpesvirus infections. 1st ednNew York: Marcel Decker; 1996. p. 1–57.

[4] Gandara-Rey JM, Pacheco-Martins JL, Gandara-Vila P, Blanco-Carrion A, Garcia-Garcia A. Primary herpetic gingivostomatitis in a 65-year-old patient. Med Oral 2002;7:180–3.
[5] Yeung-Yue KA, Brentjens MH, Lee PC, Tyring SK. Herpes simplex viruses 1 and 2. Dermatol Clin 2002;20:249–66.
[6] Neville BW, Damm DD, Allen CM. Herpes simplex virus. In: Neville BW, editor. Oral and maxillofacial pathology. 2nd ednPhiladelphia, PA: Saunders; 2003. p. 213–20.
[7] Vaughan VC, McKay RJ. Herpes simplex. In: Vaughan VC, McKay RJ, editors. Nelson textbook of pediatrics. 10th ednPhiladelphia, PA: Saunders; 1980. p. 664–9.
[8] Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, et al. Vidarabine versus acyclovir therapy of herpes simplex encephalitis. N Engl J Med 1986;314:144–9.
[9] Corey L, Fife KH, Benedetti JK, Winter CA, Fahulander A, Connor JB, et al. Intravenous acyclovir for the treatment of primary genital herpes. Ann Intern Med 1983;98:914–21.
[10] Whitely RJ, Hutto C. Neonatal herpes simplex virus infections. Pediatr Rev 1985;7:119–26.
[11] Bryston YJ, Dillon M, Lovett M, Acuna G, Taylor S, Cherry JD, et al. Treatment of first episodes of genital herpes simplex infection with oral acyclovir: a randomized double-blind controlled trial in normal subjects. N Engl J Med 1983;308:916–21.
[12] Amir J, Harel L, Smetana Z, Varsano I. Treatment of herpes simplex gingivosto-matitis with aciclovir in children: a randomised double blind placebo controlled study. BMJ 1997;21:1800–3.
[13] Raborn GW, McGraw WT, Grace M, Tyrell LD, Samuel SM. Oral acyclovir and herpes labialis: a randomised double-blind, placebo controlled study. J Ann Dent Assoc 1987;115:38–42.
[14] Mueller R, Weigand KH. The treatment of herpetic gingivostomatitis with acyclovir suspension. Der Kinderarzt 1988;19:1189–92.
[15] Hwang S, Song J, Jeong Y, Lee Y, Kang J. The efficacy of honey for ameliorating pain after tonsillectomy: a meta-analysis. Eur Arch Otorhinolaryngol 2016;27:811–8.
[16] Mansour AM, Zein W, Haddad R, Khoury J. Bullous keratopathy treated with honey. Acta Ophthalmol Scand 2004;82:312–3.
[17] Kobya H, Güdücü F. Honey prevents oral mocositis in children undergoing che-motherapy: a quasi-experimental study with a control group. Complement Ther Med 2016;29:132–40.
[18] Molan PC. The potential of honey to promote oral wellness. Gen Dent 2001;49:584–9.
[19] Simon A, Sofka K, Wiszniewsky G, Blaser G, Bode U, Fleischhack G. Wound care with antibacterial honey (medihoney) in pediatric hematology-oncology. Support Care Cancer 2006;14:91–7.
[20] Tufekci F, Erci B. The effect of parents' presence and some factors on children's pain tolerance during painful procedures. Ataturk Univ Sch Nurs J 2008;10:30–40.
[21] Rendtorff RC, Alker LC, Roberts AN. Epidemic herpetic stomatitis in an orphanage nursery. JAMA 1963;183:1068–72.
[22] Ernst E, Fialka V. Ice freezes pain? A review of the clinical effectiveness of analgesic cold therapy. J Pain Symptom Manag 1994;9:56–9.
[23] Wijesinghe M, Weatherall M, Perrin K, Beasley R. Honey in the treatment of burns: a systematic review and meta-analysis of its efficacy. J N Z Med Assoc 2009;87:429–32.
[24] Benhanifia B, Boukraa L, Hammoudi M, Sulaiman A, Manivannan L. Recent patents on topical application of honey in wound and burn management. Recent Patents Inflamm Allergy Drug Discov 2011;5:81–6.
[25] Dustmann JH. Antibacterial effect of honey. Apiacta 1979;14:7–11.
[26] Biswal BM, Zakaria A, Ahmad N. Topical application of honey in the management of radiation mucositis: a preliminary study. Support Care Cancer 2003;11:242–8.
[27] English H, Pack A, Molan P. The effects of manuka honey on plaque and gingivitis: a pilot study. J Int Acad Periodontol 2004;6:63–7.
[28] Emarah M. A clinical study of the topical use of bee honey in the treatment of some ocular diseases. Bull Islam Med 1982;2:422–5.
[29] Ozlugedik S, Genc S, Unal A, Elhan A, Tezer M, Titiz A. Can postoperative pains following tonsillectomy be relieved by honey? A prospective, randomized, placebo controlled preliminary study. Int J Pediatr Otorhinolaryngol 2006;70:1929–34.
[30] Molan P. Honey: antimicrobial actions and role in disease management. In: Ahmad I, Aqil F, editors. New strategies combating bacterial infection. Weinheim: Wiley VCH; 2009. p. 229–53.
[31] Kassim M, Achouin M, Mansor M, Yusoff K. The inhibitory effects of Gelam honey and its extracts on nitric oxide and prostaglandin E2 in inflammatory tissues. Fitoterapia 2010;81:1196–201.
[32] Al-Waili N, Boni N. Natural honey lowers plasma prostaglandin concentrations in normal individuals. J Med Food 2003;6:129–33.