Research Article

Türk Fen ve Sağlık Dergisi
Turkish Journal of Science and Health

Volume 3
Number 2
Year 2022
Pages 123-130

e-ISSN: 2717-7173 https://dergipark.org.tr/tr/pub/tfsd

Received: 18.04.2022 *Accepted:* 08.05.2022 https://doi.org/10.51972/tfsd.1104197

The Physical, Chemical and Biological Properties of Kangal Hot Spring Water and Its Use in the Treatment of Psoriasis with the Molecular Docking

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ABSTRACT:
Purpose: The aim of this study is to analyze the scientific studies on Kangal fish spa (Kangal hot spring), which has an important place for the region, and to investigate the role of minerals in water in the treatment of psoriasis with theoretical studies.
Material and Methods: The physical, chemical and biological properties of Kangal fish spa water were evaluated with the data obtained by scanning the literature. In addition, Ligands (minerals) in the spring water and targeted proteins in the selected membrane structure closest to the human body (6dvz; mus musculus membrane structure) were analyzed using Hex 8.0.0 insertion software.
Results: According to the analysis of the data of the literature review results**:**The average temperature of Kangal hot spring water is 35 °C, pH 7.42, dissolved oxygen and free carbon dioxide values are 4.4 and 8.74 mgL^{-1}. The total flow rate of the pools is 130 Ls^{-1} and its radioactivity is 6 eman. The electrical conductivity was 530 μScm^{-1} and the total mineralization range was 590.9 mgL^{-1}. According to the Hex 8.0.0 placement program, selenium and magnesium gave negative E values of E=-10.28 $kcalmol^{-1}$, E=-36.91 $kcalmol^{-1}$.
Conclusion: The literature analysis and the evaluation of the data of theoretical studies show that this spa may have positive effects in the treatment of psoriasis. It was also discovered that the Kangal fish spa met the balneological criteria and contained more of the listed therapeutic ingredients.
Keywords: *Mineral Water, Kangal Hot Spring, Psoriasis*

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INTRODUCTION

The healing waters, called hot springs, are natural formations formed by the underground water sources with geothermal energy coming to the surface. The hot springs, which have been known since the Roman period, are among the oldest alternative treatment methods used in the treatment of various diseases. Medical science, which has registered the healing effect of hot springs with the name of 'balneotherapy', also supports the use of various programs such as diet, physical activity, medical treatment, massage, aromatherapy in these facilities in order to increase the healing efficiency of natural resources. Healing waters are also used as additional treatment and medical rehabilitation of many acute and chronic diseases, depending on their physical properties and chemical structure (Košić et al., 2011). These forms of treatment and therapy have been used for centuries and remain a popular adjunctive therapy for dermatological and rheumatological diseases today. Although the favorable climate of balneotherapy thermal centers is known to have beneficial effects on psoriasis and atopic dermatitis, the hot spring waters themselves can potentially reduce skin inflammation (Huang et al., 2018). Spa treatment

should be applied regularly and carefully under the control of a doctor. Otherwise, it can cause serious problems. Those with febrile-inflammatory disease, patients with organ failure, those with any immune system disease, cancer patients, patients with bleeding or risk of bleeding, and those with acute urinary system disease cannot receive balneotherapy applications. In addition to these, it is recommended that individuals with cardiovascular disease, those suffering from common varicose veins, anemia and diabetes patients should receive these treatments by passing a doctor's control beforehand.

Thermal waters are also defined as mineral waters where the temperature measured at the outlet of the water exceeds the average local air temperature by 4 °C. Today, the concept of thermal water has been expanded to include all mineral waters that are formed within the thermal facility area, can be used for therapeutic purposes and can be consumed in the spa, regardless of the temperature at the exit points. For therapeutic applications, the temperature of the mineral water is less important than its chemistry, because the temperature of the mineral water can be changed and controlled much more easily, especially in the spa (Golušin et al., 2015). The temperature must be above 20 degrees, and there must be at least 1 gram of mineral per liter. Accordingly, hot spring waters can also be classified according to their chemical composition or temperature: bicarbonate, sulfate, sulphur, chloride and weakly mineralized trace metals or their temperatures: “cold” (<20 °C), “hypothermal” (20-30 °C), “ thermal” (30-40 °C) or “hyperthermal” (>40 °C) (Seite, 2013). Considering the classification, mineral spring water used in balneotherapy can show great differences in terms of hydrogeological origin, temperature and chemical composition (Matz et al., 2003). The use of thermal mineral water, which is a unique treatment modality in spa treatment or spa cure, is evaluated within the framework of a complex cure program together with other treatment methods (Toktaş et al., 2020). The healing waters used in balneotherapy contain minerals, etc. It can be used as a complement to various diseases due to its elements.

In Turkey has abundant resources and centers for balneotherapy, which is considered as a sub-service of thermal tourism within the scope of complementary therapy (Topsakal, 2020). The most known of these hot springs are the Dead Sea, Sivas Kangal fish spa and the blue lagoon, and it has been stated that they can be used for complementary therapy. Although psoriasis and atopic dermatitis are the most common dermatological indications; It can also be used in the treatment of many dermatological diseases such as eczema (lichen planus), skin disease in which light colored areas occur due to loss of pigment in the skin (vitiligo), ichthyosis known as fish scale disease, parapsoriasis, eczema, pityriasis rubrapilaris, alopeciaareta, acne, rosacea and prurigo. Spa treatments can be considered as an alternative treatment option in support of conventional treatments, in indications deemed appropriate by dermatologists (Kaya-Erdogan and Saracoglu, 2018). Kangal Fish Spa (Sivas-Turkey), one of the most important of these centers in Turkey and used for balneotherapy as a thermal area, is a healing water center.

Psoriasis

Psoriasis is a non-contagious chronic inflammatory dermatosis that affects 2% of the world's population. Psoriasis is characterized by recurrent episodes of red and scaly skin plaques that are sharply separated from adjacent normal skin. This disease is partly due to genetic predisposition and other environmental factors. Psoriasis is a serious skin disease that affects a person's daily life on many levels, including professional and social life. The physical and psychological effects of psoriasis can be compared to cancer, heart disease, diabetes or depression. It is possible to observe mild (<2%), moderate (2-10%) and severe (>10%) psoriasis in different people. The most common type of psoriasis is chronic plaque psoriasis or psoriasis vulgaris (Dubois Declercq and Pouliot, 2013). Currently, several treatments are available to help control psoriasis; however, current treatments may only alleviate individuals' symptoms. The choice of the most appropriate treatment depends on the patient's general health, age, co-morbidities, the form and severity of the pathology, as well as the affected body parts. In recent years, new findings on disease-related

immunological factors have fundamentally changed the treatment of psoriasis and introduced new drugs (Mrowietz et al., 2011). There is a case-controlled study in the international literature showing that Kangal hot spring is effective in the treatment of psoriasis patients, while there are various studies and anecdotal observations in the national literature reporting that it is effective in skin diseases, especially psoriasis (Sayili et al., 2007; Uysal et al., 2019; Özçelik et al., 2000; Grassberger and Hoch, 2006; Özçelik and Hayta, 2015; Duman and Şahan, 2017; Karaaslan et al., 2010a; Karaaslan et al., 2010b). With all this information, thermomineral waters that do not belong to any special water group are classified as mixed waters and the most common ones in these waters are chloride (Cl^-), sulfate (SO_4^-), bicarbonate (HCO_3^-) anions and sodium (Na^+), calcium (Ca^{+2}) and magnesium (Mg^{+2}) cations. Mixed balneological waters are named according to the dominant ions they contain. The anions and cations it carries at levels above 20% millivale give this water its name. Balneological waters with a total mineralization below 1 gL^{-1} and a natural temperature above 20 °C are called acratopegal waters, while waters with a total mineralization below 1 gL^{-1} and a natural temperature below 20 °C are called acratopegal waters (Mergen et al., 2006). In addition to the quality of the water, it has been stated in the studies that it plays a role in the emergence of its effects on the fish living in the source.

The aim of this study is to examine the physical and chemical use potential of Kangal fish spa water with a total mineralization of approximately 380 mgL^{-1} ± 30 and a low mineral content and to investigate the use of hot water. For this purpose, Ligands (minerals) in the spring water and targeted proteins in the selected membrane structure closest to the human body (6dvz; mus musculus membrane structure) were analyzed using Hex 8.0.0 insertion software.

MATERIAL and METHODS

In previous studies, trace element analyzes including major cations (Ca^{2+}, Mg^{2+}, Na^+, K^+ etc.), major anions (HCO^{3-}, SO^{4-}, Cl^-, etc.) and heavy metals were performed to determine the composition of Kangal fish spa water (Table 1). In the study, these trace elements were selected as target ligand molecules and to associate against target proteins. In addition, depending on the results of these analyzes, the beneficial effects of hot spring water on various skin diseases and especially psoriasis are discussed.

Kangal Fish Spa Water and Its Properties

Within the borders of Sivas Province; It is a spa, also known as hot spring with fish, located in the Hamam Creek (Topardiç Creek) valley, 13 kilometers northeast of Kangal District, 90 kilometers from the city (Sivas) center. Along the valley where Kangal fish spa is located, some other springs are also encountered as you go south. The one with the highest flow rate; It is the Kalkım Thermal Spring in the Kalkım Village of the Kangal District. The same species of fish living in Kangal hot thermal spring with fish are found in this spring water. The springs in Kangal fish spa, which has an altitude of 1425 m, are arranged in the north-south direction and originate from 5 different places. The hot spring water actually comes to the surface among the sandstones rather than a specific source point, and leaks occur along the stream side. The spa which was a reedy area in 1917, was put into service in 1966 with four pools and a two-storey, 16-room motel. Today, there are four parts of the hotel, six pools, 16 private bathrooms, a restaurant, a market and a tea garden (Kangal Hot Spring, 2022).

Kangal thermal spring is a hot spring used in the treatment of rheumatic diseases and psoriasis, which is one of the skin diseases in Turkey. The importance of this spa; It comes from the characteristics of the fish in the water and the chemical properties of the water. Thousands of small fish, the largest of which is 10 cm in length, live in the hot springwater. The interest in fish living in the hot springwater, which is locally defined as 'Doctor Fishes', attracts people with neurological and rheumatic diseases to this spa. The fish eat the acne and scabs of those who enter the pool, and increase the contact of the spa water with the skin. The hot spring water is beneficial for all kinds of rheumatic diseases, nervous diseases, fractures, dislocations, bruises, etc. conditions, skin and kidney diseases have a positive effect. Kangal fish spa is one of the thermal springs used as the healing water is found in

nature. According to the results of the research, Kangal fish spa area emerges as an important area in terms of both its geothermal energy potential and the possibilities of using this energy. Kangal fish spa increases the thermal characteristics of in Turkey even more. Because the Kangal fish spa is the last source of hope for people with skin diseases (psoriasis patients) who have not benefited from modern medicine until now. Irritated skin wounds or wounds in the skin tissue formed by any infection, eczema, purulent acne and psoriasis formations; It is healed by fish such as Cyprinide (from the Carp family), Cyprinion Macrostamus (Beni fish) and Garra rufa (Oily fish) with a size of 2-10 cm and their traces on the skin disappear. Thin brown, gray, beige carp and goby fish in the hot spring begin to wander around the people entering the pool and begin to clean the areas on the skin that show signs of illness. These fish, which do not have teeth, remove the raised scabs softened by the water at 36 – 37 °C and clean them until the skin becomes smooth. In order to get a positive result from the treatment, it is necessary to enter the pool three times a day for three weeks (21 days) and stay in the water for two hours. On the other hand, relaxation and rest are seen in the body with the bubbles in the water boiling from the ground and the blows of the fish on the body. The treatment is completely without side effects and absolutely no drugs are used. It has been reported that hot spring water is beneficial in rheumatic diseases, neurological (Neuralgia, Neuritis, Paralysis), orthopedic and traumatological sequelae (fractures, joint trauma and muscle diseases), gynecological problems, skin diseases, kidney stones (with drinking) and psychosomatic disorders. However, psoriasis (psoriasis) has been the disease that has made the spa the most popular in terms of treatment. In this treatment, fish are directed to psoriatic plaques (or plaques of other diseases) that soften under the influence of water. The softened scabs are removed by the fish for food, during which a small bleeding occurs and the wound is exposed to the effects of water and sunlight. This process also causes pus to drain in patients with abscesses. It has been reported that selenium, which is known to be beneficial in some diseases, is the most important factor in wound healing (Kangal Hot Spring, 2022).

Theoretical Studies

Molecular Docking

Hex 8.0.0 Docking program was used in the calculations (Abraham et al., 2022; Ghoorah et al., 2013; Ritchie, 2003). The molecular formulas of each of the elements and compounds (magnesium, chlorine, selenium, calcium) selected as Ligands in the program were drawn with the MarvinSketch 21.20 program and stored as a pdb (Protein Date Bank/PDB) file. The pdb file of the receptor protein (6dvz; mus musculus) was obtained from RCSB PDB (http://www.rscb.org/pdb). The resulting Receptor and Ligand files were transferred to Hex 8.0.0 software. The insertion energy (E value) was calculated using Hex 8.0.0 (Ghoorah et al., 2013; Ritchie, 2008).

Data Collection Tools

Previous studies have shown that the selenium concentration in the hot springwater is below the detection limit (<0.13 and <0.005 mgL^{-1}). On the other hand, in the study conducted by Gürkan (2002) the selenium concentration in the spring water was determined as 1.366 ± 0.011 mgL^{-1} by using the kinetic spectrometric method. It is known by the local people that the hot springwater is 35 + 0.5 ^{o}C and that it cures various diseases due to its chemical content, and efforts are being made to expand this treatment feature throughout the country and the world. On the other hand, it is very common to think that the fish living in the hot springwater are good for the human body because it seems like they are attacking the human body. This aspect of the spa has led researchers to obtain physical, chemical, geological, biological and clinical findings. Kangalfish spa was subjected to medical evaluation by the Ministry of Health in 2003 and was registered as a "Health Facility". Spa treatment has been used for a long time in the treatment of dermatological diseases (Kangal Hot Spring, 2022).

RESULTS

Hydrochemical analysis of hot spring mineral water

The main active ingredients of the benefits of the thermal springwaters, which are considered to be

medicinal, are the compounds or ions of the elements found in the magma layer dissolved in these waters. These elements are found in hot springwaters as much as in other waters in the world. Among the substances found in the spa waters, there are many metals and semi-metals, as well as useful minerals.Along with the elements in the soil, the substances found in all soil layers also come to the surface with the hot spring waters. According to balneological criteria, the mineral waters of Kangal thermal spring meet most of the criteria and contain more listed therapeutic ingredients.

Table 1. Hydrochemical analysis of thermal mineral water

Components	I	II	III	IV	V	VI	VII	VIII	**Average**
Temperature (°C)	35	36	35	-	-	35	35	35	35.2
pH	7.30	8.00	7.20	7.45	7.60	7.18	7.18	7.8	7.46
EC (μScm^{-1})	590	420	590	481	536.4	526	526	-	524.2
DO (mgL^{-1})	6.5	-	4.41	-	-	4.05	4.05	2.9	4.4
CO_2(mgL^{-1})	8.88	-	8.88	-	-	8.60	8.60	-	8.74
Hardness (Fr^0)	27.6	24.6	32.23	25	24.2	25.9	26	-	26.5
Cations									
Ca^{+2}($meqL^{-1}$)	3.74	3.44	2.71	4.00	3.55	3.79	3.33	2.71	3.41
Mg^{+2}($meqL^{-1}$)	1.78	1.48	3.75	1.00	1.32	1.39	1.87	3.75	2.04
Na^{+}($meqL^{-1}$)	0.87	0.73	0.17	0.193	0.72	0.63	0.23	0.17	0.47
K^{+}($meqL^{-1}$)	0.026	0.030	0.030	-	-	0.108	0.144	0.03	0.062
Anions									
HCO_3^{-}($meqL^{-1}$)	4.70	5.1	4.96	4.40	4.32	4.90	4.99	4.96	4.79
Cl^{-}($meqL^{-1}$)	0.670	0.590	0.675	0.740	0.760	0.600	0.753	0.675	0.68
SO_4^{-2}($meqL^{-1}$)	0.960	0.790	0.958	0.207	0.610	0.715	0.541	0.958	0.72
NO_2^{-}($meqL^{-1}$)	-	-	-	-	-	-	0.0022		0.002
T Anions/ T.Cations	6.33-6.42	6.48-5.68	6.59-6.66	5.35-5.19	5.69-5.59	6.22-5.92	6.29-5.57	6.59-6.66	6.19-5.98
Other Components									
NO_3^{-}($meqL^{-1}$)	-	-	-	0.006	-	-	0.72	3.32	1.35
PO_4^{-3}($meqL^{-1}$)	-	-	-	-	-	0.018	0.033	-	0.026
Fe (mgL^{-1})	-	-	0.18	0.10	0.08	0.15	<0.02	0.175	0.13
Zn (mgL^{-1})	0.016	0.020	0.02	-	-	<0.03	-	0.02	0.018
Al (mgL^{-1})	0.045	-	0.05	-	-	<0.03	-	0.05	0.045
Mn (mgL^{-1})	-	0.1	0.1	-	-	-	0.008	0.1	0.054
Cu (mgL^{-1})	-	-	0.027	-	-	-	0.02	0.027	0.024
Cr (mgL^{-1})	-	-	0.1	-	-	-	<0.03	0.1	-
Pb (mgL^{-1})			0.1	-	-	0.03	<0.04	-	0.07
Se (mgL^{-1})	-	-	1.30	-	-	-	-	1.3	-
Br (mgL^{-1})	0.675	0.270	-	-	-	-	-	0.675	0.473
F (mgL^{-1})	0.50	0.27						0.27	0.385

P: Parameters, 1: I.T.U. Medicine Faculty (İstanbul), Aug. 1974; 2: Mineral Resarchand Exploration (Ankara), June 1982; 3: C.U. Science Faculty (Sivas), Ann. Ave. 1987; 4: Kangal Hot Spring Administration (Sivas), July 1991; 5: Bank of Provincs Lab. (Ankara), Nov. 1992; 6A: H.U. Karst Wat. Res. Cen. Lab. (Ankara), April 1993; 6B: C.U. Env. Eng. Dept. (Sivas), April 1993; 6C: C.U. Env. Eng. Dept. (Sivas), May 1993; 7A: C.U. Env. Eng. Dept. (Sivas), Sept. 2001; 7B: H.U. Karst Wat. Res. Cen. Lab. (Ankara), Sept. 2001; 7C: S.U. Agricult. Faculty Res. Lab. (Konya), Sept. 2001

Table 2. Molecular Docking data of minerals found in Kangal Spring Water

E Total ($kcalmol^{-1}$)						
Receptor / Ligands	**Calcium**	**Phosphate**	**Iron**	**Chlorine**	**Magnesium**	**Potassium**
6dvz	-36.91	-135.53	-1.49	-41.37	-36.91	-15.81
Receptor / Ligands	**Sulfate**	**Selenium**	**Flor**	**Nitrite**	**Nitrate**	
6dvz	-135.53	-10.28	-1.49	-92.32	-102.45	

To evaluate the quality of medicinal waters, balneological criteria including the following elements are applied: water temperature, pH value, total mineralization, followed by the presence of macro components i.e. ions, sodium, calcium, magnesium, hydrocarbonates, chlorides, sulfates and finally iodine, bromine, lithium, fluorine, strontium, meta silicon and meta boric acid and the presence of micro components of carbon dioxide, hydrogen sulfide, nitrogen and oxygen from gases are important. Average temperature is 35 °C, pH 7.42, dissolved oxygen (DO) and free carbon dioxide values are 4.4 and 8.74 mgL^{-1}, respectively. Average temperature 35 °C, pH 7.42, dissolved oxygen (DO) and free carbon dioxide values are 4.4 and 8.74 mgL^{-1}, respectively. The total flow rate of the pools was determined as 130 Ls^{-1}, electrical conductivity (EC) 530 μScm^{-1}, total mineralization range 590.9 mgL^{-1} and radioactivity 6 eman. The water composition of the Kangal fish spa water is given in Table 1 below (Değirmenci and Ünver, 2021; Özcelik et al., 2000; Özçelik and Hayta, 2015).

Molecular Docking

Demonstrates the binding affinity between minerals and targeted proteins (membrane proteins) using the Hex 8.0.0 docking software. The height of the binding affinity is measured in relation to the height of the negative E value. When the data are examined, it is seen that all minerals have negative E values. In addition, the highest negative E values against 6dvz (cell membrane); phosphate and sulfate are E= -135.53 $kcalmol^{-1}$, nitrite and nitrate are E=-92.32 $kcalmol^{-1}$, E=-102.45 $kcalmol^{-1}$, respectively. The molecular docking of the minerals found in the spring water is shown in Table 2 below.

DISCUSSION

Springwater is an isothermal-hypotonic and oligometallic mineral water with an average electrical conductivity (EC): 530 μScm^{-1}, CO_2 8.70 mgL^{-1},and dissolved oxygen value (DO) 4 mgL^{-1} (Değirmenci and Ünver, 2021). The electrical conductivity of 530 μScm^{-1} indicates a high dissolved ion content. The level of balneotherapy effect is proportional to the increase of the relevant factors. Therefore, the total mineralization range was found to be 590.9 mgL^{-1} and classified as high mineral content water (Kangal- Turkey Spas Portal, 2022). Calcium, magnesium and bicarbonates are dominant in the spa water. Neither the chemical values nor the temperature (35 ± 1 °C) of the water show seasonal changes. The hot spring water is clear, colorless and odorless. Due to the slightly alkaline water, it causes swelling and softening of the epidermis, increasing the elasticity of the skin, and has a positive effect on various skin and gynecological diseases. When evaluated in terms of dominant anions, the most common cation was Ca^{+2}, followed by Mg^{+2}, Na^{+} and K^{+}, respectively. The most common anion was HCO_3^{-} followed by SO_4^{2-} Cl^{-}, respectively. Total NO_3^{-} content indicates soil pollution. According to the analyses made, NO_3 values were found to be quite low and this value can be accepted as an indicator of the cleanliness of the water.

The amount of selenium in Kangal hot springwater was found to be 1.3 mgL^{-1}. Selenium and other elements; with its antioxidant, antiproliferative and immunomodulatory properties, it has two effects on skin diseases; systemic effect (by drinking) and local effect (penetration into the skin) (Özçelik and Hayta, 2015). According to the results of molecular docking, it is seen that the minerals in Kangal hot springwater have binding affinities to the cell membrane. Among the negative E values found, the minerals with the highest affinity; Phosphate and Sulfate are E= -135.53 $kcalmol^{-1}$, Nitrite and Nitrate are E=-92.32 $kcalmol^{-1}$, E=-102.45 $kcalmol^{-1}$, respectively. At the same time, it was understood that trace elements such as selenium, magnesium and fluorine, which are good for psoriasis and found in Kangal hot springwater, have affinity for binding to the cell membrane by molecular docking. With these binding affinity values, the degree of adhesion to the skin has also been proven. Selenium and other elements have proven that these effects can show a good prognosis in the treatment of psoriasis.

CONCLUSION

As a result of the analyzes and evaluations, it has been revealed that the water of the Kangal hot spring and the fish in the hot spring show positive results in the treatment of many diseases. It was discovered that elements such as selenium,

magnesium, zinc and fluorine found in the hot spring water, which was examined in accordance with the purpose of the research, have an affinity with the cell membrane as a result of molecular docking. This discovery showed that Kangal hot springwater has a significant healing effect on skin diseases, especially psoriasis. The curative effect of Kangal hot springwater on skin diseases has been proven by our studies and other studies, and it is also promising for many diseases whose treatment has not yet been discovered.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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