RESEARCH PAPER

Expression of some HSP genes in Hydatids isolated from cattle, sheep and human

Ibtihal Ahmed Issa Al-Mousawi1, Sarmad Awad Mozan AL-Asadi1

[1] Department of Biology, College of Education for Pure Sciences, University of Basrah, Basrah, Iraq

mailto:elkawakibsyam@gmail.com **dalyla413@gmail.com**

Abstract

Echinococcosis is a zoonotic disease transmitted between animals and humans, caused by the larval (metacestode) stage of the parasite Echinococcus granulosus. Heat shock proteins c) constitute a highly conserved group of proteins present across all forms of life. Like many parasites, E. granulosus undergoes a complex life cycle involving multiple developmental stages and host transitions. A key adaptive mechanism in parasites is the upregulation of heat shock proteins (HSPs), which play essential roles in stress response and cellular homeostasis.This study aimed to investigated of some HSPs sub cellular located in different organules in the cell . In this study, a total of 160 hydatid cyst samples were collected from infected livers between November 2022 and May 2023. These included 60 samples from cattle, 60 from sheep, and 20 surgically isolated from human livers.The bioinformatic results are analyzed of both nuclear and mitochondrial DNA (mtDNA) from the sheep strain (G1), retrieved from the NCBI genome database, identified 20 distinct HSP genes. Gene expression analysis focused on *hsp 90-5, hsp 70-5*, and *hsp 60*, which represent HSPs with distinct subcellular localizations. The results consistently showed higher expression levels of these genes in the germinal layer compared to the protoscoleces across all host species. Notably, *hsp 90-5* exhibited the highest upregulation in the germinal layer, while *hsp 70-5* showed the lowest expression in the protoscoleces. These findings underscore the potential importance of HSPs in supporting the metabolic activity and stress resilience of the germinal layer and may offer insights into molecular mechanisms critical for parasite development and survival within intermediate hosts.

How to cite this article: Al-Mousawi IAI, AL-Asadi SAM. Expression of Some HSP Genes in Hydatids Isolated from Cattle, Sheep and Human. Int J Drug Deliv Technol. 2026;16(24s): 289-295. DOI: 10.25258/ijddt.16.24s.34

1. Introduction

Echinococcosis is a zoonotic disease that occurs in humans and animals. It is caused by the metacestode stages of the genus Echinococcus, family Taeniidae, which infects a wide range of domestic and wild animals [1,2] .

The life cycle of E. granulosus has two hosts. Carnivores are the definitive hosts, especially dogs. Adult worms live in their small intestine. Humans and ruminants, both domestic and wild, are intermediate hosts [3,4]. Echinococcus is a tropical disease listed by the World Health Organization (WHO). It is widespread in environments with varying conditions, whether hot, polar, tropical or subtropical. The parasite usually survives, and most parasites undergo complex life cycles that involve differentiation through different stages of development and transmission through two or more hosts. Passage through many different hosts and environments exposes pathogens to sudden changes in growth conditions and harsh conditions. Many parasites have developed adaptations and resistance mechanisms in order to survive [5,6,7].

One of these mechanisms is through increased expression of a specific group of proteins known as heat shock proteins (HSPs). HSPs constitute a highly conserved group of proteins present across all forms of life. Their primary role is to function as molecular chaperones, as described by Lindquist and Craig (1988). These chaperones are part of a protein family that facilitates the proper folding of nascent polypeptides and, in certain instances, assists in their assembly into oligomeric structures (Narberhaus 2002). .They are considered a response to stress conditions in the subarctic and harsh climatic regions [8]. Reported that HSPs may play a major role in the virulence and differentiation of parasites [9] In addition to its important role in the development of the parasite [10] as well as their adaptation to the host, is fundamental [5]. Also indicated that HSPs are one of the causes of disease progression and infection [11] This study aimed to characterize the expression patterns of selected heat shock protein (HSP) genes with distinct subcellular localizations in hydatid cysts from various intermediate host species.

2. Methods

2.1 Sample collection

The hydatid cyst samples were collected during the period from November 2022 to May 2023 from livers infected with hydatid cysts from different intermediate hosts (cattle , sheep and human). 60 livers infected with hydatid cysts from cattle and 60 livers infected with hydatid cysts from sheep were collected from the central Basra and Thi Qar slaughterhouse, in addition to collecting 20 surgically isolated hydatid cysts. The contents of the hydatid cyst (hydatid fluid and protoscoleces) were withdrawn following the method [12]. Figure 1

Fig . 1. Hydatid cysts isolation from livers of study species

A- Liver of cattle infected with hydatid cyst
B- Liver of sheep infected with hydatid cyst
C- Hydatid cyst isolated from human liver
D- Germinal layer of Hydatid cyst isolated from human liver

2.2RNA extraction

Ribonucleic acid (RNA) was extracted from the protoscoleces or germinal layer and isolated from cattle , sheep, and human hydatid cysts using the GENEzolTMTriRNA Pure Kit. This extraction kit is prepared by the manufacturer from Geneaid / Taiwan. The manufacturer's steps were followed to estimate the RNA concentration, by using the Nanodrop device.

2.3cDNA syntesis

To manufacture cDNA, 1 µg of RNA was used using the GoTaq®2-Step RT-qPCR System kit, according to the program provided by the manufacturer (Bioneer).

2.4 qPCR

Specific primers were designed to target the gene expression of some heat shock proteins (*HSP60, HSP70_5, HSP90_5,* and Actin 2). Using the Primer3Plus program, the primers used in the gene expression study were ordered from Macrogene and are shown in Table (1).

Table .1. Specific Primers Used in this Study

Primer	5` ----------`3
Actin-2_F	CGAGCAGGAAATGATAACG
Actin-2_R	GAACAGGGCTTCAGGACA
HSP60_F	CCAGGATGCCTGTGTTCTTT
HSP60_R	CCTCAGCAACAATGACGAGA
HSP70_5F	AAGGGAGGTATTTGGGATGG
HSP70_5R	CCACTCCACCGTCTGTAGGT
HSP90_5F	AGCTCTGCACCCACTGATCT
HSP90_5R	GGATCCTTTGCGATTTTGAA

The qPCR reaction was performed in a total volume of 20 µL, consisting of 10 µL of GoTaq® qPCR Master Mix, 1 µL of forward primer, 1 µL of reverse primer, 6 µL of cDNA template, and 2 µL of nuclease-free water. Reactions were carried out using a real-time PCR thermal cycler under the following conditions: an initial pre-denaturation step at 95 °C for 2 minutes (1 cycle), followed by 45–50 cycles of denaturation at 95 °C for 30 seconds, annealing at 60 °C for 30 seconds, and extension at 72 °C for 30 seconds. A melt curve analysis was subsequently performed with the following steps: 95 °C for 1 minute, 55 °C for 30 seconds, and a final step at 95 °C for 30 seconds.

2.5 Statistical analyses

The t-test and one-way ANOVA were used for statistical analysis.

3-Results

3.1 Bioinformatics analysis of the genome of *Echinococcus granulosus* strain G1

The results of the bioinformatics analysis of the genomes of the nuclear DNA and mitochondrial (mt DNA) of the sheep strain (G1) at the National Centre for Biotechnology Information (NCBI) showed that this strain possesses 20 proteins of the HSPs . Their cellular locations ranged between the cytoplasm and the mitochondria in addition to the secretory peptide, as shown in the table.2

Table.2 Cellular Localization of HSPs in *E. granulosus* Strain G1

Protein	Subcellular location	Accetion number
HSP90B-5	SP*	XP_024350600.1
HSP70-1	Cytoplasme	XP_024345034.1
HSP70-2	Cytoplasme	XP_024346002.1
HSP70-3	Cytoplasme	XP_024346587.1
HSP70-4	Cytoplasme	XP_024347541.1
HSP70-5	Cytoplasme	XP_024349384.1
HSP70-6	Cytoplasme	XP_024350984.1
HSP70-7	Cytoplasme	XP_024351093.1
HSP70-8	Cytoplasme	XP_024346388.1
HSP70-9	Cytoplasme	XP_024346586.1
HSP70-10	Cytoplasme	XP_024348044.1
HSP70-11	Cytoplasme	XP_024351092.1
HSP60	mTP	XP_024353311.1
HSP10	mTP**	XP_024346601.1
HSP36	Cytoplasme	XP_024353253.1
HSP11B	Cytoplasme	XP_024355835.1

*/ Secretional protein **/ Mitochondrial protein

3.2 Gene expression of the components of the hydatid cyst

3.2.1Gene expression of *hsp 90-5* gene

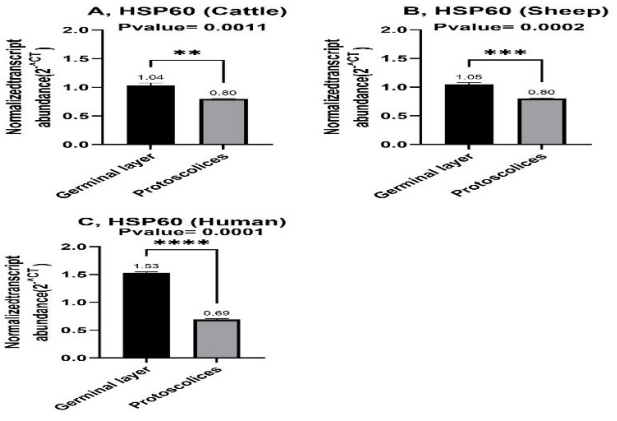
The gene expression analysis of ***hsp 90-5*** in hydatid cysts isolated from humans, sheep, and cattle infected with *E.granulosus* revealed a consistent and statistically significant upregulation of mRNA transcription in the germinal layer compared to the protoscoleces across all host species (P = 0.0001). This observation highlights the essential role of this molecular chaperone in the metabolically active and proliferative germinal tissue of the parasite.

Among the three hosts studied, the highest expression level of ***hsp 90-5*** was observed in human-derived hydatid cysts, where transcript abundance reached 1.51 in the germinal layer compared to 0.15 in the protoscoleces—an approximate 10.06-fold increase. This substantial elevation may reflect heightened physiological or immunological stress encountered by the parasite in the human host, necessitating an increased chaperone response to maintain protein homeostasis.

In sheep, the transcript level in the germinal layer was 1.48, while in protoscoleces it was 0.81, indicating a 1.83-fold increase. Similarly, in cattle, the germinal layer exhibited a transcript abundance of 1.17, whereas the protoscoleces showed a lower level of 0.38, corresponding to a 3.08-fold increase.

These inter-host differences in expression magnitude suggest that *E. granulosus* may differentially regulate ***hsp 90-5*** expression depending on the host environment, potentially in response to varying immune pressures or metabolic conditions. Nevertheless, the consistent overexpression of ***hsp 90-5*** in the germinal layer across all hosts underscores its pivotal function during larval development and cellular proliferation.

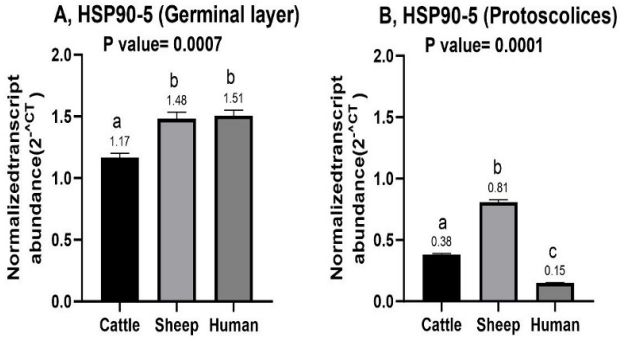
Collectively, these findings not only provide insight into the host-dependent transcriptional dynamics of *E. granulosus*, but also propose *hsp90-5* as a potential molecular target for therapeutic interventions aimed at disrupting parasite development within the host. As shown in the figure (2) .



Figure(2) **gene expression of *hsp 90-5* gene in the studied species**

The results of the current study showed that there are significant differences in the gene expression of the *hsp 90-5* gene isolated from the germinal layer isolated from the intermediate hosts under study (cattle, sheep and human), as the mRNA transcription rates reached 1.51, 1.17 and 1.48 respectively. The highest transcription rate was in the germinal layer isolated from the hydatid cyst of the infected human liver. The lowest transcription rate was in the germinal layer isolated from the hydatid cyst of the infected cattle liver. As shown in the figure (3).

The results of the study also showed that there are significant differences in the gene expression of the *hsp 90-5* gene isolated from the protoscoleces isolated from the intermediate hosts under study (cattle, sheep and human). The mRNA transcription rates reached 0.15, 0.38 and 0.81, respectively. The highest mRNA transcription rate was in the protoscoleces isolated from the hydatid cyst of the liver of infected sheep. The transcription rate was 0.81, while the lowest transcription rate was in the protoscoleces isolated from the hydatid cyst of the liver of infected human. The transcription rate was 0.15, as shown in the figure (3).



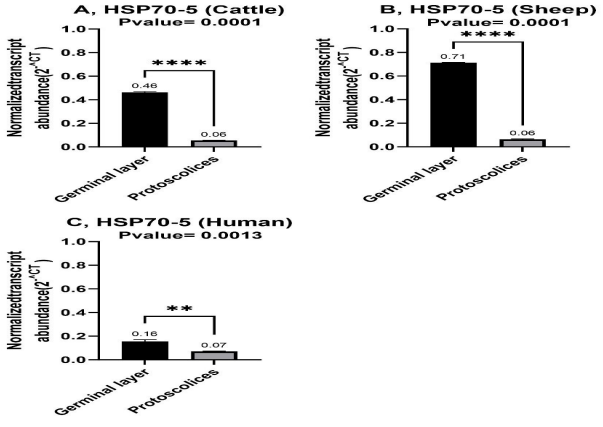
Figure(3) A comparative assessment of gene *hsp 90-5* expression between the germinal layer and protoscoleces for the species under investigation

3.2.2Gene expression of *hsp 70-5* gene

The comparative analysis of ***hsp 70-5*** gene expression across hydatid cysts isolated from three host species—humans, sheep, and cattle—demonstrated a consistent pattern of significantly higher mRNA transcription levels in the germinal layer compared to the protoscoleces. This suggests a conserved role for the ***hsp 70-5*** molecular chaperone in supporting active metabolic and proliferative processes in the germinal layer across host species.

In human-derived cysts, the ***hsp 70-5*** transcript abundance reached 0.16 in the germinal layer, compared to 0.07 in the protoscoleces, reflecting an approximate 2.29-fold increase. In sheep, the germinal layer showed the highest transcript level among the three hosts at 0.71, whereas the protoscoleces exhibited a markedly lower expression at 0.06, yielding a nearly 11.83-fold increase—the most pronounced differential among all groups. Cattle-derived samples exhibited intermediate expression levels, with the germinal layer at 0.46 and the protoscoleces at 0.06, resulting in a 7.67-fold increase. This pattern not only confirms the elevated requirement for ***hsp 70-5*** in the germinal layer but also reveals host-specific variation in expression intensity. Notably, sheep exhibited the highest overall fold-change between tissue types, which may suggest a stronger physiological demand for chaperone-mediated protein regulation in the germinal layer of sheep cysts. In contrast, the human samples, while still showing statistically significant upregulation in the germinal layer, presented the lowest absolute values and fold-change among the hosts studied. This variation could reflect host-parasite interaction dynamics or differences in host immune responses and metabolic environments.

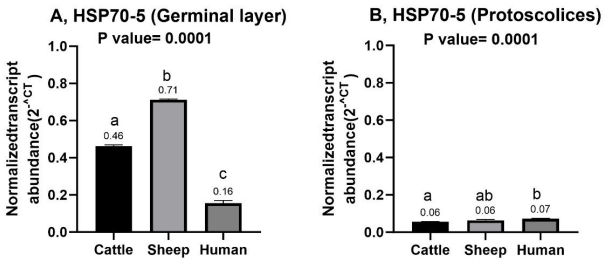
Collectively, these findings reinforce the functional importance of HSP70-5 in maintaining protein homeostasis under cellular stress conditions, particularly in the parasite's proliferative germinal layer, and highlight the potential of this gene as a target for diagnostic or therapeutic interventions in echinococcosis**.** As shown in figure (4).



Figure(4) **gene expression of *hsp 90-5* gene in the studied species**

The results of the current study showed that there are significant differences in the gene expression of the *hsp 70-5* gene isolated from the germinal layer isolated from the intermediate hosts under study (cattle, sheep and human), as the mRNA transcription rates reached 0.16, 0.46 and 0.71 respectively. The highest transcription rate was in the germinal layer isolated from the hydatid cyst of the infected sheep liver. The transcription rate reached 0.71 .The lowest transcription rate was in the germinal layer isolated from the hydatid cyst of the infected human liver. The transcription rate reached 0.16 . As shown in the figure

The results of the study also showed that there were significant differences in the gene expression of the *hsp 70-5* gene isolated from the protoscoleces isolated from the intermediate hosts under study (cattle, sheep and human). The mRNA transcription rates reached 0.07, 0.06 and 0.06, respectively. The highest mRNA transcription rate was in the protoscoleces isolated from the hydatid cyst of the liver of infected human liver , which reached 0.07. while the lowest transcription levels were in the protoscoleces isolated from the hydatid cyst of the cattle and sheep infected liver, which had the same transcription rates, reaching 0.06. As shown in the figure(5).



Figure(5) A comparative assessment of gene *hsp 70-5* expression between the germinal layer and protoscoleces for the species under investigation

3.2.3Gene expression of *hsp 60* gene

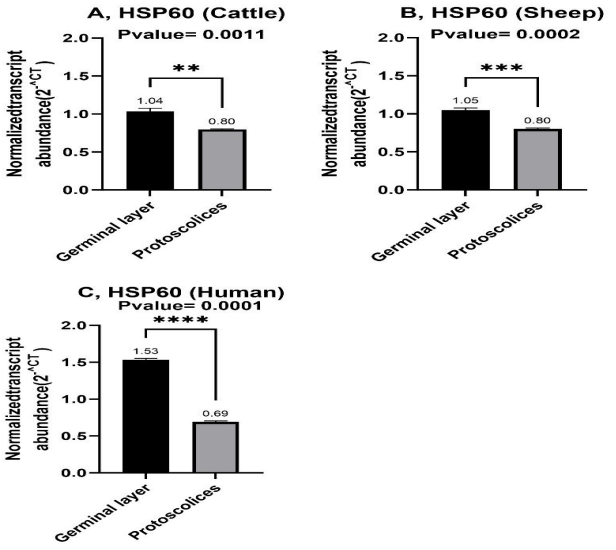
The gene expression analysis of *hsp 60* in hydatid cysts obtained from cattle, sheep, and humans infected with Echinococcus granulosus demonstrated a consistent and statistically significant upregulation in transcript abundance within the germinal layer compared to the protoscoleces across all host species. This pattern suggests a conserved and potentially critical role for *hsp 60* in the metabolically active tissues of the parasite, likely related to protein folding and cellular stress management.

In human-derived cysts, *hsp 60* exhibited the highest transcriptional activity among all host groups, with a normalized transcript level of 1.53 in the germinal layer versus 0.69 in the protoscoleces, indicating an approximate 2.22-fold increase. In sheep, the gene expression was also elevated in the germinal layer (1.05) relative to the protoscoleces (0.80), corresponding to a 1.31-fold difference. A similar pattern was observed in cattle, where transcript levels were 1.04 in the

germinal layer and 0.80 in the protoscoleces, reflecting a 1.30-fold increase.

These findings emphasize the essential requirement for HSP60 in the germinal layer, likely due to the high demands for protein homeostasis, cellular proliferation, and stress regulation in this biologically active region of the parasite. The more pronounced difference observed in human samples could reflect host-specific immune pressures or environmental conditions that induce a heightened stress response, thereby stimulating increased chaperone expression.

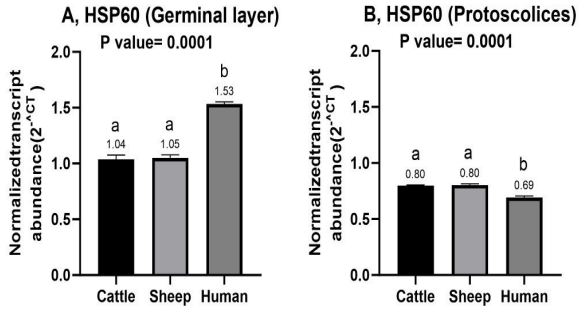
Collectively, the data support the notion that HSP60 plays a central role in parasite survival and adaptation, particularly within the germinal layer, and suggest that it may serve as a valuable molecular target for diagnostic or therapeutic strategies aimed at controlling cystic echinococcosis. As shown in figure (6).



Figure(6) **gene expression of *hsp 60* gene in the studied species**

The results of the current study showed that there are significant differences in the gene expression of *hsp 60* genes isolated from the germinal layer isolated from the intermediate hosts under study (cattle, sheep and human). The mRNA transcription rates reached 1.53, 1.04 and 1.05, respectively. The highest mRNA transcription rate was in the germinal layer isolated from the hydatid cyst of the infected human liver. The transcription rate reached 1.53, while the lowest transcription rate was in the germinal layer isolated from the hydatid cyst of the infected cattle liver. The transcription rate reached 1.04, as shown in the figure

The results of the study also showed that there were significant differences in the gene expression of the *hsp 60* gene isolated from the protoscoleces isolated from the intermediate hosts under study (cattle, sheep and human). The mRNA transcription rates reached 0.69, 0.80 and 0.80, respectively. The highest mRNA transcription rate was in the protoscoleces isolated from the hydatid cyst of the liver of infected cattle and sheep, which had the same transcription rates, reaching 0.80, while the lowest transcription levels were in the protoscoleces isolated from the hydatid cyst of the human infected liver , which reached 0.69, as shown in the figure (7).



Figure(7) A comparative assessment of gene *hsp 60* expression between the germinal layer and protoscoleces for the species under investigation

Discussion

Bioinformatic analysis of the nuclear and mitochondrial genomes of *E. granulosus* strain G1 (sheep strain) revealed the presence of 20 distinct genes encoding heat shock proteins (HSPs). The identification of this number of HSP-encoding genes highlights the critical role of the chaperone system in the parasite's biology, particularly given its complex life cycle and exposure to fluctuating environmental conditions within both intermediate and definitive hosts (Craig *et al*., 2017). The exclusive localization of all HSP genes within the nuclear genome underscores the parasite's reliance on centralized gene expression mechanisms for the production of these proteins. This is consistent with the general pattern observed in eukaryotes, where most HSPs are transcribed from nuclear DNA, translated in cytosolic ribosomes, and subsequently trafficked to their functional destinations, including the mitochondria (Finka *et al*., 2016).

The differential abundance of Heat Shock Proteins (HSPs) between the germinal layer and the protoscoleces of the hydatid cyst reflects the distinct functional and environmental adaptations associated with each stage of the parasite's life cycle. These differences underline the parasite's remarkable capacity to adjust to its varying microenvironments and physiological requirements.

1. Adaptation to Environmental Stress

The germinal layer is exposed to numerous stressors, including fluctuations in temperature, nutrient deprivation, and immune attacks from the host. These dynamic and unstable conditions stimulate the production of high levels of HSPs, such as HSP70 and HSP90, which are crucial for protecting cells from oxidative stress, repairing damage, and preventing apoptosis. Conversely, the protoscoleces reside in a relatively stable environment within the hydatid fluid, where they are shielded from significant environmental fluctuations, resulting in a lower requirement for these protective proteins.

2. Metabolic Requirements and Cellular Regulation

As an active site of asexual reproduction and differentiation, the germinal layer exhibits high metabolic activity and frequent cellular division. Such intense biological activity necessitates elevated levels of HSPs to ensure proper protein folding, cellular repair mechanisms, and stress adaptation. On the other hand, the protoscoleces remain in a metabolically dormant or low-activity state, awaiting transmission to a new host, which explains their reduced reliance on HSPs.

3. Immune Responses and Stress Mitigation

The germinal layer is directly involved in countering host immune responses. HSPs play a pivotal role in immune evasion mechanisms and in inducing cellular responses against stress. In contrast, the protoscoleces are encapsulated within a protective cyst wall, which minimizes their direct exposure to the host's immune system

Highlighted that the germinal layer is responsible for producing the laminated layer and that the hydatid fluid contains essential nutrients required for the growth and development of the larval cyst[13]. Furthermore, they noted that the development of protoscoleces depends on the formation of brood capsules derived from the germinal layer. The hydatid fluid itself is a biologically diverse mixture, composed of both parasite and host proteins, which supports the parasite's survival and growth.

The variation in HSP levels between the germinal layer and the protoscoleces underscores the functional adaptations of each stage to its respective environment. The germinal layer relies on high levels of HSPs to sustain its metabolic and reproductive functions under stressful conditions, whereas the protoscoleces economize energy by downregulating HSPs, ensuring their survival until they infect a new host.

The protoscoleces inhabit a stable environment characterized by the near absence of stress-inducing conditions. This lack of environmental stress has resulted in a marked reduction in the gene expression levels of HSP 70 and HSP 60 proteins. Such stability minimizes the activation of stress-response pathways, leading to the observed downregulation of these heat shock proteins[14] . They can be utilized as primary protein antigens[15,16,17].I t is hypothesized that HSP60 and HSP70 may serve as potential vaccine candidates offering protective immunity against infections[18].

Conclusion

The observed variation in gene expression levels of heat shock proteins (HSPs) between developmental stages (germinal layer and protoscoleces)and across different host species reflects a functional specificity of these proteins depending on both the developmental context and the host environment. This differential expression pattern suggests an adaptive response of the parasite to host type and site of infection. These findings imply that elevated levels of HSPs may serve not only as indicators of cellular stress adaptation but also as potential biological markers of host-dependent parasitic behavior. Consequently, HSPs may represent promising molecular targets for the development of novel therapeutic or diagnostic strategies against cystic echinococcosis.

Acknowledgments

This research project is supported by the Department of Biology, College of Education for Pure Science, University of Basrah, Basrah, Iraq. It is a part of the PhD graduation requirements.

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