INTRODUCTION

The closely related protozoan parasites, *Toxoplasma gondii* and *Neospora caninum* have an indirect life cycle with carnivores as the definitive hosts, distributed worldwide and can infect a wide range of animal species. In the host, *T. gondii* and *N. caninum* can cause abortion or neonatal mortalities (Anderson et al., 1991; Dubey, 2003; Guo et al., 2015). While toxoplasmonic encephalitis is a life-threatening central nervous system infection observed in the later stages of HIV infection (Luft and Remington, 1992), *N. caninum* result in neurologic alterations in dogs (Barber and Trees, 1996). As a result of either acute infection or reactivation of infection *T. gondii* in infection can be life threatening for congenitally infected infants, immunocompromised, and immunodeficient patients (Frenkel and Escajadillo, 1987; Chintana et al., 1998; Luft and Remington, 1988; Aspinall et al., 2003). In animals, both parasites infection result in significant reproductive losses, and hence economic losses, (Faria et al., 2007; Donahoe et al., 2015).

In previous surveys from Egypt, *T. gondii* and *N. caninum* antibodies were demonstrated in the sera from asymptomatic pregnant women (Ibrahim et al., 2009a; El-Shqanqery et al., 2017; Ibrahim et al., 2017, 2018), chickens (El-Massey et al., 2000; Ibrahim, 2013, 2016), ducks, pigeons, sheep (Dubey et al., 2003; Ibrahim, 2016; Ibrahim et al., 2017, 2018), camels, and water buffalo (Hilali et al., 1998; Dubey et al., 1998).

In cattle and water buffalos, *N. caninum* can affect animal productivity (Chryssafidis et al., 2011), resulting in reproductive losses such as abortions and neonatal mortality (Dubey et al., 2007; Chryssafidis et al., 2015). Furthermore, viable *T. gondii* was isolated from naturally...
infected aborted bovine fetuses (Canada et al., 2002). Therefore, both diseases are considered important economic diseases in animals, and zoonosis of Toxoplasma results in a variety of clinical manifestations in humans.

In the Egyptian markets, cattle and water buffaloes are representing the main sources of red meat (Alboghdady and Alashry, 2010). Several previous studies reported the unpropitious consequences of Toxoplasma and Neospora on the host performance and health status (Mahboub et al., 2013; Donahoe et al., 2015; El-Sayed et al., 2016; Didiano et al., 2020). In the current study, our objective was to estimate the biochemical effects of Toxoplasma gondii and Neospora caninum on naturally infected cows and water buffalos in Menoufia Province, Egypt.

MATERIALS AND METHODS

ETHICS STATEMENT
This study was performed after getting permission from the Institutional Animal Ethical Committee, Menoufia University, Egypt (approval ID: MUFS/F/IM/2/17).

BLOOD SAMPLES
Out of five hundred examined bovine samples, one hundred and ten blood samples, normal, healthy and naturally infected with Toxoplasma and/or Neospora, were collected from water buffalo and cow (63 water buffalo samples, 47 cow samples). The samples were incubated at room temperature for one hour, centrifuged at 3000 rpm for 15 minutes and then sera were collected and stored at −20°C until analysis.

EXPERIMENTAL DESIGN
Collected serum samples were divided into 13 groups (7 groups of water buffalo’s samples and 6 groups of cow’s samples) according to the status of infection. The infection status was confirmed by highly specific TgSAG2 and NcSAG1 based ELISA (Ibrahim et al., 2009a).

WATER BUFFALO’S SERUM SAMPLES
Group 1: Normal, healthy serum samples (n=10); Group 2: Chronically infected serum samples with T. gondii (positive for IgG antibodies) (n=9); Group 3: Acutely infected serum samples with T. gondii (positive for IgM antibodies) (n=11); Group 4: Chronically infected serum samples with N. caninum (positive for IgG antibodies) (n=11); Group 5: Acutely infected serum samples with N. caninum (positive for IgM antibodies) (n=10); Group 6: Chronically infected serum samples with T. gondii and N. caninum mixed infection (n=8); Group 7: Acutely infected serum samples with T. gondii and N. caninum mixed infection (n=4).

COW’S SERUM SAMPLES
Group 1: Normal, healthy serum samples (n=10); Group 2: Chronically infected serum samples with T. gondii (positive for IgG antibodies) (n=7); Group 3: Acutely infected serum samples with T. gondii (positive for IgM antibodies) (n=7); Group 4: Chronically infected serum samples with N. caninum (positive for IgG antibodies) (n=10); Group 5: Acutely infected serum samples with N. caninum (positive for IgM antibodies) (n=10); Group 6: Chronically infected serum samples with T. gondii and N. caninum mixed infection (n=3). In the current study no mixed T. gondii and N. caninum acute infection was detected in cow’s samples.

BIOCHEMICAL ANALYSIS
Aspartate transaminase (AST) activity, alanine transaminase (ALT) activity, and alkaline phosphatase (ALP), as they produced intracellular and their elevated serum levels indicate hepatocytes damage, were measured using kinetic kits (Human Diagnostic Kits, Germany). Also total protein, albumin, total bilirubin, and direct bilirubin were detected using colorimetric method kits (Diamond Diagnostics kits, Egypt). Blood urea and serum creatinine, indicate kidney damage, were examined using (Diamond Diagnostic kit, Egypt). Uric acid was measured using Spinreact diagnostics kit (Spain). Lipid profile (cholesterol, triglycerides, and high density lipoprotein [HDL]) was measured using Spinreact diagnostic kits (Spain). Low density lipoprotein (LDL) was measured indirectly using the Friedewald formula which incorporates total cholesterol, HDL and triglyceride concentrations: LDL (mg/dL) = total cholesterol (mg/dL) − HDL (mg/dL) − triglyceride (mg/dL)/5 (Friedewald et al., 1972; Tremblay et al., 2004). The serum globulin level was calculated by subtracting the obtained serum albumin concentration from the obtained serum total protein concentration (Ibrahim et al., 2019). Finally, the inflammatory marker C-reactive protein (CRP) was detected using Biosystems diagnostics kits (Spain).

STATISTICAL ANALYSIS
Using SPSS, data were subjected to statistical significance tests using one-way analysis of variance (ANOVA), followed by post hoc analysis of group differences that was accomplished by the least significant differences (LSD) test; P<0.05 was considered to be statistically significant.

RESULTS
The results of water buffalos in the present study showed that there was a significant increase in serum AST activity in samples with chronic infection of T. gondii while there is no significant change during chronic infection of N. caninum or mixed chronic infection of N. caninum and T. gondii. On the level of ALP activity, a significant increase was detected in all chronically infected groups compared
with the control group. There is also a significant increase in cholesterol, triglyceride and LDL in all chronically infected groups as compared with the control group. Chronic mixed infection resulted in an evaluation of HDL levels without any significant change when compared to the control healthy group. Finally, there is a significant increase in CRP compared with the control group in the chronically infected water buffalo's samples. No significant changes were detected in all other examined parameters in comparison with the control group (Table 1).

Table 2 revealed that there is a significant increase in serum ALP activity in all acutely infected groups when compared to the control group. Moreover, a significant increase was detected on the activity of AST in the acutely infected N. caninum group as compared to control group. The activity of this enzyme was elevated in the acutely infected T. gondii group and acutely mixed infection without any significant changes. Urea, as a kidney function parameter, showed a significant increase in the Toxoplasma infected group during the acute infection in water buffalo's samples. Cholesterol and LDL level were significantly elevated in the acutely N. caninum infected group when compared to the control group. Higher level of cholesterol and LDL was detected in T. gondii and mixed infection during the acute infection without any significant differences. Triglycerides and CRP showed a significant increase in all acutely infected groups in comparison with the control healthy group. No significant changes were detected in all other examined parameters in comparison with the control group.

Table 1: Biochemical analysis of chronically infected water buffalos with toxoplasmosis and/or neosporosis.

| Parameters   | Control | T. gondii +ve IgG | N. caninum +ve IgG | Mixed infection +ve IgG |
|--------------|---------|-------------------|--------------------|------------------------|
| AST (U/L)    | 102.75±4.05 | 129.68±7.52*     | 112.22±4.14       | 95.80±6.29             |
| ALT (U/L)    | 57.90±2.30   | 59.52±2.66       | 59.52±2.66        | 51.94±3.12             |
| ALP (U/L)    | 80.62±8.06   | 149.60±17.80*    | 133.20±6.59*      | 128.00±4.43*           |
| Albumin (g/dl)| 4.08±0.07    | 3.98±0.06        | 3.89±0.07         | 3.85±0.11              |
| Total protein (g/dl) | 6.75±0.19 | 6.89±0.13       | 7.04±0.10         | 6.58±0.21              |
| Globulin (g/dl) | 2.71±0.17    | 2.91±0.15        | 3.15±0.12         | 2.73±0.16              |
| Total bilirubin (mg/dl) | 0.52±0.02  | 0.53±0.03       | 0.53±0.03         | 0.59±0.04              |
| Direct bilirubin (mg/dl) | 0.11±0.01   | 0.13±0.01       | 0.20±0.05         | 0.13±0.02              |
| Urea (mg/dl) | 45.65±0.90   | 49.16±1.56       | 48.76±0.78        | 49.11±1.81             |
| Creatinine (mg/dl) | 1.24±0.02   | 1.27±0.02       | 1.28±0.02         | 1.20±0.07              |
| Uric acid (mg/dl) | 3.74±0.15    | 3.75±0.10        | 3.69±0.13         | 3.32±0.23              |
| Cholesterol (mg/dl) | 96.82±9.32  | 149.75±14.68*   | 157.45±10.34*     | 168.69±12.85*          |
| Triglyceride (mg/dl) | 54.17±9.49  | 155.75±33.35*   | 98.16±14.68*      | 125.14±25.40*          |
| HDL (mg/dl)   | 36.29±2.20   | 38.96±2.04       | 36.63±1.46        | 43.60±1.95             |
| LDL (mg/dl)   | 61.00±8.06   | 84.51±8.88*      | 99.89±7.89*       | 111.12±9.37*           |
| CRP (mg/l)    | 2.88±0.97    | 11.14±2.4*       | 12.75±2.64*       | 14.40±4.07*            |

Data are expressed as: Means ± SE. * Indicates significant difference (P < 0.05).

Table 2: Biochemical analysis of acutely infected water buffalos with toxoplasmosis and/or neosporosis.

| Parameters   | Control | T. gondii +ve IgM | N. caninum +ve IgM | Mixed infection +ve IgM |
|--------------|---------|------------------|-------------------|------------------------|
| AST (U/L)    | 102.75±4.05 | 115.55±5.99     | 124.56±7.04*      | 112.85±10.11           |
| ALT (U/L)    | 57.90±2.30   | 60.18±3.63       | 61.54±4.12        | 56.40±2.85             |
| ALP (U/L)    | 80.62±8.06   | 130.78±8.83*     | 132.49±11.06*     | 111.52±5.97*           |
| Albumin (g/dl)| 4.06±0.08    | 3.93±0.07        | 3.89±0.08         | 3.95±0.09              |
| Total protein (g/dl) | 6.77±0.19 | 6.91±0.09       | 6.66±0.21         | 6.37±0.32              |
| Globulin (g/dl) | 2.70±0.17    | 2.98±0.11        | 2.77±0.20         | 2.42±0.25              |
| Total bilirubin (mg/dl) | 0.52±0.02  | 0.58±0.03       | 0.57±0.03         | 0.58±0.05              |
| Direct bilirubin (mg/dl) | 0.11±0.01   | 0.15±0.01       | 0.15±0.02         | 0.13±0.03              |
| Urea (mg/dl) | 45.65±0.90   | 51.51±1.33*      | 49.24±1.55        | 44.13±2.25             |
| Creatinine (mg/dl) | 1.24±0.02   | 1.27±0.02       | 1.22±0.02         | 1.11±0.12              |
| Uric acid (mg/dl) | 3.74±0.15    | 3.76±0.13        | 3.81±0.11         | 3.28±0.26              |
| Cholesterol (mg/dl) | 96.82±9.32  | 137.93±12.23    | 161.22±17.95*     | 144.05±29.94           |
| Triglyceride (mg/dl) | 54.17±9.49  | 112.61±17.61*   | 107.09±11.35*     | 91.83±21.09*           |
| HDL (mg/dl)   | 36.29±2.20   | 38.57±1.35       | 43.03±1.26        | 39.58±2.25             |
| LDL (mg/dl)   | 61.00±8.06   | 85.18±8.63       | 100.50±16.48*     | 86.11±26.95            |
| CRP (mg/l)    | 2.49±0.61    | 12.67±2.33*      | 12.75±2.64*       | 8.00±2.00*             |

Data are expressed as: Means ± SE; * Indicates significant difference (P < 0.05).
The results of cows in the present study illustrated that there is a significant increase in serum AST, ALT activity only in mixed chronically infected samples with no significant increase in other chronically infected groups as compared to the control group. ALP activity was increased significantly in T. gondii and N. caninum chronically infected groups compared with the control group, while the activity of this enzyme was elevated in the mixed chronically infected group without any significant change. Total bilirubin showed a significant increase in the chronically N. caninum infected group when compared to control group. Urea and creatinine levels were elevated in the mixed chronically infected group without any significant changes when compared to the control group. Uric acid showed a significant increase in chronically T. gondii infected group. Cholesterol and triglyceride showed a significant increase in chronically N. caninum infected group, while there is an elevation in those parameters in chronically T. gondii infected group and mixed chronically infected group without any significant changes. Finally, LDL and CRP showed a significant increase in all chronically infected groups when compared with control group (Table 3).

**Table 3:** Biochemical analysis of chronically infected cows with toxoplasmosis and/or neosporosis.

| Parameters          | Control   | T. gondii +ve IgG | N. caninum +ve IgG | Mixed infection +ve IgG |
|---------------------|-----------|------------------|--------------------|------------------------|
| AST (U/L)           | 56.31±2.14| 48.72±2.62       | 49.51±3.44         | 111.93±16.00*         |
| ALT (U/L)           | 29.61±1.96| 29.07±2.47       | 27.89±1.93         | 43.37±8.36*           |
| ALP (U/L)           | 109.90±18.54| 161.17±18.51*    | 193.89±27.64*      | 136.63±38.72          |
| Albumin (g/dl)      | 3.92±0.09 | 3.80±0.16        | 3.74±0.15          | 3.96±0.08             |
| Total protein (g/dl)| 7.09±0.27 | 7.69±0.20        | 7.50±0.22          | 6.94±0.37             |
| Globulin (g/dl)     | 3.17±0.23 | 3.89±0.31        | 3.75±0.16          | 2.98±0.44             |
| Total bilirubin (mg/dl) | 0.63±0.03    | 0.63±0.05    | 0.80±0.04*         | 0.51±0.02             |
| Direct bilirubin (mg/dl) | 0.16±0.01     | 0.18±0.02   | 0.21±0.02          | 0.11±0.02             |
| Urea (mg/dl)        | 34.90±1.54 | 40.10±0.58       | 39.25±1.56         | 43.97±5.69            |
| Creatinine (mg/dl)  | 0.83±0.06 | 0.86±0.10        | 0.89±0.06          | 1.18±0.06             |
| Uric acid (mg/dl)   | 3.84±0.10 | 4.39±0.23*       | 4.11±0.13          | 3.53±0.33             |
| Cholesterol (mg/dl) | 119.91±13.04| 159.03±26.27    | 206.62±22.85*      | 145.50±9.85           |
| Triglyceride (mg/dl)| 56.09±7.35| 63.01±16.42      | 166.00±26.19*      | 77.13±18.97           |
| HDL (mg/dl)         | 37.81±1.57| 39.03±0.75       | 39.53±1.40         | 38.10±2.99            |
| LDL (mg/dl)         | 59.68±6.67| 125.40±22.45*    | 159.76±18.93*      | 91.97±10.44*          |
| CRP (mg/l)          | 3.08±1.1 | 10.00±2.97*      | 15.00±2.78*        | 12.00±0.00*           |

Data are expressed as: Means ± SE. * Indicates significant difference (P < 0.05).

**Table 4:** Biochemical analysis of acutely infected cows with toxoplasmosis or neosporosis.

| Parameters          | Control   | T. gondii +ve IgM | N. caninum +ve IgM |
|---------------------|-----------|------------------|--------------------|
| AST (U/L)           | 56.31±2.14| 50.29±4.78       | 51.69±3.15         |
| ALT (U/L)           | 29.61±1.96| 28.80±1.90       | 32.11±2.59         |
| ALP (U/L)           | 109.90±18.54| 140.20±21.58     | 210.38±30.42*     |
| Albumin (g/dl)      | 3.92±0.90 | 4.02±0.18        | 3.87±0.10          |
| Total protein (g/dl)| 7.09±0.27 | 7.63±0.20        | 7.55±0.20          |
| Globulin (g/dl)     | 3.17±0.23 | 3.61±0.20        | 3.69±0.16          |
| Total bilirubin (mg/dl) | 0.63±0.03    | 0.67±0.05    | 0.72±0.04          |
| Direct bilirubin (mg/dl) | 0.16±0.01     | 0.17±0.01   | 0.16±0.01          |
| Urea (mg/dl)        | 33.48±1.96| 46.34±3.00*      | 39.36±2.44         |
| Creatinine (mg/dl)  | 0.83±0.06 | 0.89±0.08        | 0.75±0.04          |
| Uric acid (mg/dl)   | 3.84±0.10 | 3.84±0.09        | 3.75±0.11          |
| Cholesterol (mg/dl) | 119.91±13.04| 185.43±25.37    | 139.60±13.94       |
| Triglyceride (mg/dl)| 50.96±2.42| 49.96±10.04      | 46.28±3.27         |
| HDL (mg/dl)         | 37.81±1.57| 41.74±1.53       | 39.49±1.52         |
| LDL (mg/dl)         | 59.68±6.67| 141.44±22.97*    | 94.83±14.10*       |
| CRP (mg/l)          | 2.91±0.97 | 14.40±4.07*      | 11.14±2.42*        |

Data are expressed as: Means ± SE. * Indicates significant difference (P < 0.05).
Table 4 showed that there is a significant increase in serum ALP activity in the acute N. caninum infected group as compared with the control group. There is an elevation in ALP level in acutely T. gondii infected group without any significant change. Moreover, urea was significantly increased in acutely T. gondii infected group, while there was an elevation in the acutely N. caninum infected group without any significant change as compared with the control group. Higher level of cholesterol was detected in T. gondii and N. caninum during the acute infection without any significant difference compared with the control group. Finally, LDL and CRP showed a significant increase in all acutely infected groups compared with the control group. No significant changes were detected in all other examined parameters in comparison with the control group.

DISCUSSION

In the present study, we investigated the effects of T. gondii and N. caninum infection on water buffalos and cow’s health through examining the changes in some biochemical parameters of the infected animals in comparison with normal healthy animals. These parameters give an indication about the effects of these causative agents on animals’ health and performance.

In the current work, toxoplasmosis and neosporosis increase the activity of serum liver enzymes. In the examined bovine samples, ALP activity was elevated obviously in T. gondii, N. caninum and mixed chronically and acutely infected groups compared with the control group. Moreover, there is a significant increase in serum AST, ALT activity in mixed chronically infected cow samples, and a significant elevation in AST activity in samples with chronic infection of T. gondii and acute infection of N. caninum in water buffaloes. These findings were in line with that indicated by (Suzuki., 1971; Portugal et al., 2004; Al-Kaysi et al., 2010; Al-Hussary and Al-Zuhairy, 2010; Alekish et al., 2017; Didiano et al., 2020), who found that the activities of AST and ALT were increased in T. gondii and N. caninum infected animals. In humans, the results of Toxoplasma positive patients showed a significant elevation in the liver enzymes: AST, ALT, and ALP in the sera compared with negative patients (Al-Khamesi et al., 2016; El-Sayed et al., 2016). These changes may be due to the liver damage caused by Toxoplasma and/or Neospora infection, which increased the release of the liver enzymes in the serum. Previous studies recorded that Toxoplasma or Neospora infection resulted in extensive damage in the liver cells (Blais et al., 1993; Calderaro et al., 2009; Donahoe et al., 2015; El-Sayed et al., 2016; Alekish et al., 2017).

In the current study, urea level was elevated obviously in N. caninum acutely infected bovine samples. Furthermore, urea, uric acid and creatinine levels were increased in T. gondii and the mixed chronically infected bovine samples as compared with control samples. The elevation in the urea concentration may due to Toxoplasma deleterious effects on the kidney which decrease the excretion of urea from the body and subsequently increased its serum level (Mahboub et al., 2013). Toxoplasma and Neospora were found in the kidneys of the infected animals and led to pathological changes in their tissues (Fayed et al., 2004; Hammouda et al., 2006; Gharadaghi et al., 2012; Donahoe et al., 2015).

The present study revealed that Toxoplasma and Neospora infection increased serum cholesterol, triglyceride, and LDL levels in chronically infected animals and cholesterol and LDL levels in acutely infected animals. Our finding was in agreement with previous studies (Stockham and Scott, 2002; Mahboub et al., 2013; Didiano et al., 2020). Also previous reports found that parasitic and HIV infection elevates lipoproteins like HDL, LDL and total cholesterol levels (Djoumessi, 1989; Rimland et al., 2006). Toxoplasma uses the host metabolic products for its own metabolic pathways (Al-Kennany, 2007). It is well known that cholesterol is synthesized in the endoplasmic reticulum through the main enzyme of the mevalonate pathway, hydroxymethylglutaryl-CoA reductase and further utilized by the cell for synthesis of cholesterol derivatives or membrane biogenesis. Previous microarray analysis using T. gondii–infected human foreskin fibroblasts showed up-regulation of key genes involved in the mevalonate pathway and cholesterol synthesis (Blader et al., 2001). This included an increase in expression level of hydroxymethylglutaryl-CoA reductase (Blader et al., 2001). Nishikawa et al. (2011) detected that in macrophages the growth of intracellular T. gondii was contributed to the host cholesterol synthesis.

Our study demonstrated that Toxoplasma and/or Neospora infection increased the inflammatory marker CRP levels in acutely and chronically infected animals when compared to the control animals. This elevation may due to the inflammation related effect of these pathogens in different tissues of the infected animals. Several previous studies recorded the abilities of these parasites and their related proteins to enhance the production of many pro-inflammatory mediators such as interleukin-6, interleukin-8, tumor necrosis factor alpha and nitric oxide during their infection (Ibrahim et al., 2009b; Ibrahim and Scott, 2002; Mahboub et al., 2013; Didiano et al., 2020). These changes may be due to the liver damage caused by Toxoplasma and/or Neospora infection, which increased the release of the liver enzymes in the serum. Previous studies recorded that Toxoplasma or Neospora infection resulted in extensive damage in the liver cells (Blais et al., 1993; Calderaro et al., 2009; Donahoe et al., 2015; El-Sayed et al., 2016; Alekish et al., 2017).

CONCLUSION

Both toxoplasmosis and neosporosis negatively affected the liver function, lipid profile and inflammatory status, which reflect harmful consequences on dairy bovine animals’ health and performance. Further studies will be needed to define the mechanisms of these consequences.
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AUTHOR’S CONTRIBUTIONS

HMI designed the study. NMB, HMI and AMA performed most of the experiments, analyzed and interpreted the data. NMB and HMI wrote the first version of the manuscript. HMI, AAHA and NMB assisted during the analysis and interpretation of data and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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