The manuscript is now well improved; however, some major corrections are still necessary.

General Comments:

Please refine the language and check the grammar mistake very carefully throughout MS.

Still, some experiments are incomplete, should provide the data of three samples in all experiments and should explain the proper reason for a particular study design especially in animal experiments.

Specific Comments:

Line 17. (DSC), X-ray diffraction (XRD)..(FTIR) were used to identify stable chemical structure: Readers already know the application of these techniques so no need to explain, the author should write the results/observation got from these experiments. For instance: FTIR data revealed the changes in the secondary structure of protein due to chitosan and TPP crosslinking.

Line 60 delete “further”

Line 70 Chemical crosslinking of chitosan, such as: Chemical crosslinking of chitosan by crosslinkers such as..

Line 72. It can be used to prepare cross-linked chitosan particles with good biocompatibility.: The authors discuss only TPP and chitosan, should discuss the interaction between chitosan and collagen; collagen and TPP; and how TPP crosslinks both chitosan and collagen.

Line 80 closely arranged, thin in diameter and interwoven into a network with typical characteristics of type I collagen and triple helix structure,: This observation is not enough or inappropriate to conclude the features like type I and triple helix structure.

with typical characteristics of type I collagen and triple helix structure: Where is it seen in Fig.1a?

chitosan presented a small pore structure: What is the flat like structure with holes behind the globules. Is it also chitosan?

Line 83 might be the: might be the

Line 92-96. The maximum swelling degree of … after incubation for 0.5 h in pH 1.2 buffer: Combine in one sentence.

Line 111. Figure 2.: Collagen (alone) and chitosan (alone) results missing in this experiment
Line 117. Mention the figure number. Firstly, chitosan had an endothermic peak at 67.2 oC (Fig. 3),….

Line 168. aged mice groups compared with the young control group: Explain the main reason for choosing young and old age mice in this experiment.

Line 183 Table 1. contain same amount of collagen and chitosan : This means 200g/kg.bw of collagen and 200g/kg.bw of chitosan? So 400g/kg.bw of total complex sample administered? Give the specific dosage of t complex sample.

Line 244 Figure 8. Expression of tyrosinase gene in B16 melanoma cells. (M) Marker, (A) Control, (B-E) Collagen 12.5, 25, 50, 100 μg/ml; (F-I) Collagen/chitosan complexes 12.5, 25, 50, 100 μg/ml.: Data for Chitosan Group were missing here. The maker band is hard to observe. Do the amendment.

304 a little of the collagen/chitosan complexes powder: 10 mg of the collagen/chitosan complexes powder…Write the exact sample quantity like this.

Line 309. 40 aged (10 months old) mice: Change to “Ten months old mice (40 numbers)”…

Lines 314-315 Forty aged mice were randomly divided into four groups. There were 10 mice in each group, half male and half female. They were blank aging control group: Change to “Male and female mice were randomly divided into four groups (10 mice/group):control (give details, saline?), chitosan (200 mg/kg.d), fish skin collagen (200 mg/kg.d) and collagen/chitosan group (200 mg/kg.d). All the samples were administered orally by gavage (give the details of gavage size, brand, company)”.

The author should
refine this manuscript like the above.

Lines 317-320. The mice in the chitosan group were given 200 mg/(kg·d) …content of collagen by gavage.: Delete these sentences

Another 10 young mice, half male and…: Confusing, the authors mentioned 40 mice and divided into four groups (10 per group), then how they selected another 10 mice? So a total of 50 mice? What is the blank aging control group and control group? Are they same or different?

Line 366 Total RNA extraction: Trizol reagent: First explain how the cells were treated with your samples for mRNA experiment then discuss RNA extraction protocol.

The author should provide the microscopic (wither light or fluorescent images) images of B16 melanoma cells treated with and without your samples. Because there is no evidence that the authors used these cells in their experiments.

If possible provide some pictures of 1) animal experiments (some animal photos during the experiment) and 2) collagen/chitosan complexes to help the reader to understand your work more clearly.

The conclusion part is now convincing.

Next time, Kindly Provide a separate attachment, describing the authors’ response to all the reviewers’ comments for easy tracking. It is very hard to cross-check the revision.